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PHARMACEUTICALS AND INSECTICIDES AT  
I.G. FARBEN PLANTS  
ELBERFELD AND LEVERKUSEN

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COMBINED INTELLIGENCE OBJECTIVES  
SUB-COMMITTEE

Enclosure A  
Naval Report No. X2887-5 4T



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PHARMACEUTICALS AND INSECTICIDES AT I.G. FARHEN PLANTS  
ELBERFELD AND LEVERKUSEN

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~~C O N F I D E N T I A L~~

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a. INTRODUCTION

Organization

I. G. Werk, Wuppertal-Elberfeld is a branch of I. G. Farbenindustrie A.G. It is pertinent at this point to outline the general organization of the parent firm. The executive committee of the Board of Directors consists of Schmitz (head of the organization, who succeeded Bosch), von Schnitzler (sales), Gajewski (fibers), Hörlein (pharmaceuticals), von Knieren (legal, patents), ter Meer (Ludwigshafen), Schneider (Leuna).

There were 16 other Directors, some of whom are now dead or retired; Kuehne - at Leverkusen, now being retired; Ambros; Brüggemann, at Leverkusen (legal); Bürgin, at Bitterfeld; Bütefisch, at Leuna; Hölfinger, Ilgner; Jacobi, now retired; Jähne (Chief Engineer); Lautenschläger, at Hoechst; Mann (sales), at Leverkusen; Oster, retired; Otto, retired; Weibel, deceased, was Sales Director for Far East; Weber-Andreas, deceased; Wurster; Müller-Cunradi, newly appointed during the war. Heberland has been appointed to succeed Kuehne. The I. G. also has about 100 other members of the firm called "Directors". These men have the right to sign legally binding documents for the I. G., provided another Director also signs.

The I. G. is divided geographically into:

Nieder Rhein - includes Elberfeld, Leverkusen,  
Dormagen, Uerdingen, Knapsack,  
Duisburger Kupferhütte.

Mittel Rhein

Ober Rhein

Mittel Deutschland

The I. G. owns 75% of the Hüls Company, the remainder belonging to Ibernica. The Elberfeld Company has three I.G. Directors, namely, Hörlein, Lutter, and Schönhöfer.

Staff at Elberfeld

Prof. Heinrich Hörlein is general head of Elberfeld. The principal scientific personnel under his direction follows:

Pharmazeutische Betriebe

Direktor Dr. Lutter

Dr. Heimhold

Dr. Rietz  
Dr. Bauer  
Dr. Bergdolt  
Dr. Gänzler  
Dr. Gundlach

Dr. Hoch  
Dr. Jaeger  
Dr. Otto Leuchs  
Dr. Schultz  
Dr. Wiegand

#### Pharmazeutische Betriebslaboratorien

Dr. Dörr  
Dr. Deichsel

Dr. Haensel  
Dr. Geth

#### Analytische- und Untersuchungs-Laboratorien

Dr. Loth  
Dr. Tettweiler  
Dipl. Jng. Ebert

Frl. Dr. Leonhard  
Frl. Dr. Widmann

#### Chemisch-wissenschaftliche Laboratorien

Direktor Dr. Schönhöfer  
Dr. Mietzsch  
Dr. Andersag  
Dr. Behnisch  
Dr. Breitner  
Dr. Hiltmann  
Dr. Klarer  
Dr. Kls  
Dr. Linsert  
Dr. Friedrich Leuchs

Dr. Mauss  
Dr. Meiser  
Dr. Pöhl  
Dr. Salzer  
Professor Dr. Schmidt  
Dr. Schrader  
Dr. Schütz  
Dr. Timmler  
Dr. Westphal  
Dr. Wieder

#### Physikalisches Laboratorium

Dr. Lode

#### Chemotherapeutisches Laboratorium

Professor Dr. Kikuth  
Frl. Dr. Bock

Frl. Dr. Madrow

#### Bakteriologisches- und experimentell Pathologisches Laboratorium

Professor Dr. Domagk  
Frl. Dr. Brömmelhues

Dr. Gottsacker  
Dr. Hackmann

#### Pharmakologisches- und Gewerbehygienisches Laboratorium

Professor Dr. Weese  
Professor Dr. Gross

Dr. Hecht

## Physiologisches Laboratorium

Professor Dr. Weyland  
Dr. Auhagen  
Frl. Dr. Barrink  
Dr. Bohne  
Dr. Döttl

Dr. Friedrich  
Dr. Lange  
Dr. Ripke  
Dr. Schenek  
Dr. Ziegler

## Poliklinik

Dr. Richeler

## Ingenieur-Abteilung

Oberingenieur Dahm  
Dr. Andres

Jag. Bergmann  
Dipl. Jag. Gloss

## Elberfeld Products

I. G. Elberfeld manufactures pharmaceuticals in bulk. These are then sent to Leverkusen for making into salable products - tablets, ampoules, etc. Leverkusen also does some bulk pharmaceutical manufacturing, including salicylic acid, aspirin, the sulfonamides, Atebrine, Istizin, various veterinary products, as well as insecticides. Leverkusen also handles the pharmaceutical sales for the I.G. Behringwerke and for Hoechst. Chemical sales are handled through Frankfurt. Some finishing of tablets and ampoules has also been done in Western Prussia, at Preussisches Stargard. Such finished products are made also at Marburg and Hoechst. No finished products are made at Elberfeld. Elberfeld is the original plant of the Bayer Company, which originally also made dyestuffs.

A list of products manufactured, and stated by Director Hörlein to be complete as of 21 April 1945, is as follows:

## Pharmaceutische Präparate

Abasin	Laktoflavin
Abrodil	Luminal
Acidol-Pepsin	Luminaletten
Acidum acetylosalicylicum	Luminal-Natrium
Acidum diethylbarbituricum	Manetol
Acidum phenyläethylbarbituricum	Marfanil (Mesudin)
Acaprin	Marfanil-(Prontalbin)
Acranil	Mesudin (Marfanil)
Adalin	Mitigal
Afridolseife	Murnil

Ascaridol	Natriumdiaethylbarbituricum
Antileprol	Natriumnitrit-Tabletten
Antimosan	Natriumphenylaethylbarbituricum
Aricyl	Neo-Uliron
Aspiphenin	Neo-Stibosan
Aspirin	Nikotinsäureamid
Atebrin	Optarson
A. T. 10	Ortizon
Atepe (Atebrin comp.)	Padutin
Avertin "flüssig"	Pardinon
Bayer 205 (Germanin, Naganol)	Paretten
Bedermin	Per-Abrodil
Betaxin	Periston
Butolan	Phanodorm
Cafaspin	Phanodorm-Calcium
Campolon	Plasmochin
Carbopulbit	Presinol
Certuna	Priovit
Chinoplasmin	Prolan
Cignolin	Prominal
Coffeminal	Prominaletten
Compral	Prontalbin
Coryfin	Prontosil u. Prontosil solubile
Cyren	Protargol
Detavit	Sajodin
Dontalol	Salol
Elloform	Selvorol
Eleudron	Septazin
Endojodin	Solarson
Eumydrin	Solustibosan
Evipan	Spirosal
Evipan-Natrium	Sulfapyridin
Fuadin	Tannigen
Germanin, Naganol (Bayer 205)	Tenosin-Liquor
Gravitol	Theocin-Natr. acetic
Helisen	Theominal
Helmitol	Tibatin
Hexamethylenetetramin	Tolid
Hexeton-Lösungen	Trivitan
Immetol	Tutocain
Impletol	Uliron
Istizin	Unden-Dragees and Lösungen
Jacopral	Vaduril
Jothion	Veronal und- Natrium
Kaliumsulfoguaiajolicum	Vigantol
Kresival	Vogan
	Yatren
	Zephirol

## Technische Produkte

T. C.-Harz (Hochschmelzendes Cumaronharz)

Aethylcellulose

Benzylcellulose

Cellapret (Celluloseessigsäures Natron)

Aldol-a-Naphtylamin

Vulkacit 576 und - extra (Kondensationsprodukt von Anilin  
bezw. p-Toluidin mit Aethylpropyl-  
acrolein)

Beschleuniger FP (Kondensationsprodukt von Formaldehyd mit  
p-Toluidin)

Thiuram (Tetramethylthiuramdisulfid)

Vulkacit 1000 (o-Tolybiguanid)

Wirkstoffe für Ceresan Trocken-und Nassbeize (Methoxyaethyl-  
Hg-silicat bezw. Chlorid)

Vulkacit - H (Hexamethylentetramin)

Vulkanol-B (Kondensationsprodukt von Benzylchlorid mit  
Naphtalin)

Sintol-T (ein technisches Mitigel)

Castrix-Körner (Wirkstoff: Dimethylaminochlorpyrimidin)

Zellio-Körner (Wirkstoff: Thalliumsulfat)

Filtragol und Filtral (Peptinspaltende Enzyme)

Belvitan (Wirkstoff: S-Indolessigsäures Kalium)

Obviously, the greater volume of products manufactured at Elberfeld consists of pharmaceuticals. The limited smaller group of technical products made there is mainly an outgrowth of the work on pharmaceuticals, for example, vulcanizers, rubber ageing products, insecticides, plasticizers. Prof. Hörlein stated that synthetic rubber was discovered there as well as acetyl cellulose.

## Personnel

Practically all the technical personnel were available at Elberfeld at the time of our visit. Domagk was absent and was stated to be in the Berlin area. A limited number of the scientific staff had been called to military service. Most of these had been allowed to return to the laboratories even though of military age. Research was allowed to proceed, although various members of the staff emphasized that many difficulties were encountered. The Elberfeld plant normally employs about 1200 people. Recently, this has included about 250 foreigners, who were not technical employees, although some were chemical operators.

## Condition of the Plant

The plant was in excellent condition, showing very little damage. A few artillery shells struck on about 13 April, just before the occupation. There had been no bombs inside the plant. It last operated on Saturday, 14 April. American troops came on 16 April. No technical records were said to have been evacuated. The T-Force seized some records, mostly of manufacturing methods, which a few days later were turned over to our CIOS Team.

At the time of our visit it was found that enough coal was on hand to operate 10 to 14 days. Normally 10,000 to 12,000 pounds of steam per month were produced; 1600 to 1700 tons of coal per month during the summer and somewhat more in the winter were required, which normally produced 1000 kwh electric power.

### Government Domination of Operations

It was stated by Director Hörlein and others that the German government had not taken over any part of the plant during the war or had operated any division of it. Hörlein stated that the I. G. had been charged with helping to prepare for the war, even by German newspapers. He claimed that this was not true; their main products were prepared for the general good long before the war, such as Atebrin in 1932, and the sulfonamides a few years later. As a matter of fact, he stated, they had had no help from the government, but rather great difficulty. Early during the Nazi Regime the government brought pressure against vivisection, which was so necessary for the testing of their new drugs and the control of their old ones, and Hörlein almost was placed in a concentration camp for his opposition to the Nazi policy in this regard. Later, that policy changed. Hörlein stated that at Elberfeld their work was done for their country and for the world, and their results were made generally available.

### Chemical Warfare

Hörlein stated that no chemical warfare or anti-gas products were manufactured at Elberfeld. Gas warfare research was done at Berlin by the War Ministry. Hörlein stated that he had advised the Nazi government not to use gas. He stated that he was not informed as to production of gas by other I. G. branches.

### Collaboration with the Japanese

Hörlein stated that before the war the I. G. Elberfeld

merely sold some products to the Japanese, then they established a Bayer subsidiary in Japan and later made tablets and filled ampoules there from materials supplied by Germany. The amounts shipped to Japan were small. Hörlein stated that they did not wish to work closely with Japanese, who were neither fair nor honest in their commercial dealings and did not respect legal rights such as patents. The I. G. often had to sue in Japan to protect their patents, and even then lost sound cases in some instances. The Japanese negotiated with Elberfeld for a license to use a process for the manufacture of thiamine, but this was not consummated.

### Laboratory Organization

Members of the research staff appear to have been given considerable freedom in the choice of their problems. Young graduates of the universities are assigned problems under the direction of more experienced men, and remain assistants for several years; when they show capacity they are given more freedom in their work. Opinion was expressed by several department heads that a new man is not likely to contribute much during the first five years of his employment.

Schönhöfer stated that according to the rules research staff members are supposed to submit written reports once a month. Actually, they are more likely to do so once a year. Schönhöfer stated that he submits no regular written reports to Hörlein. Hörlein and the department heads (about thirteen in all) meet on Saturday mornings for two or three hours to discuss any plant and research policy matters. No seminars or general meetings of the research staff are held. Their chemists are obtained from various laboratories, including particularly those of Prof. Hans Fischer of the Technische Hochschule in Munich; Prof. Wieland, University of Munich; Prof. Windaus, University of Göttingen, and some from Prof. Kuhn, Heidelberg; and Prof. Schipf, at Darmstadt.

At the start a new Ph.D. receives 3500 to 4000 marks annual salary. Physicians are paid better at the start in the I.G.; but if the chemist discovers something worthwhile, his income will exceed that of the physician. He may even receive more than a Director.

Each research worker who has become established is likely to have 2 assistants in his laboratory. One of these is probably technically trained and the other may be a male or female handy assistant. In the case of Dr. Weese, he has

six technical assistants who are girls with 2 years of training as "technische assistenten". There are 3 such schools for girls in Germany--at Cologne, Halle, and Tübingen.

### Research Budget

The annual research budget at Elberfeld is about three million marks. 85% of this is spent for work on pharmaceuticals. It is estimated that each research worker costs from 30,000 to 40,000 marks per year, including all clerical assistance, library, overhead, etc.

### Salaries

The salaries of the most important Elberfeld department heads are augmented by variable bonuses paid annually. These depend upon the importance of the contributions of each man in the past year. They are as follows:

	<u>Salary</u>	<u>Bonus</u>
Weese	13,000 marks	22,000
Kikuth	15,000	29,000
Schönhöfer	24,000	22,000
Lutter	24,000	31,000
Weyland	13,000	11,000
Domagk	15,000	53,000

### Library Facilities

Elberfeld has a good scientific library with 3 trained librarians who abstract literature, make searches, etc. Part of the original Kekulé Library is here.

### Equipment

The research laboratory equipment seems adequate, and up-to-date. Pharmacological laboratories are spacious and modern with excellent equipment. The organic research laboratories are roomy, rather old, with lead top desks and heavy line shafts above the desks for stirring. Each desk is supplied with line vacuum and also 2mm line vacuum for distillations.

### Research Program

Hörlein stated that during the war a good deal of their research was directed along the lines of sulfanomides and

similar products, particularly for the treatment of anaerobic infections, which was difficult at times because of lack of animals and food. The staff appears to consider future research on malaria and on anti-biotic agents such as Penicillin to be especially worthy of attention.

From the standpoint of available personnel, intact facilities, and general capacity, it appears that Elberfeld is in a position to continue its work whenever it is permitted to do so.

## b. SULFONAMIDES AND SULFONES

The sulfonamides are manufactured at both Elberfeld and Leverkusen. The principal products of this class are Marfanil ( $\text{NH}_2\text{CH}_2\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2$ ), Prontosil Rubrum, Prontosil Album (Sulfanilamide), Eleudron (Sulfathiazole), Sulfapyridine. Sulfadiazine ("Debenal") has so far not been manufactured. The scale of production seems somewhat limited compared to U. S. production. Greatest interest appears to be focused on Marfanil and its combinations.

At Elberfeld the intermediate sulfonchloride is made in four 1000 liter kettles. The reaction product is run into a tile-lined 6000 liter square tank having a lead pipe containing brine for cooling. The wet intermediate sulfonchloride is used for condensation with the appropriate amine.

### Eleudron (Sulfathiazole)

Rate of production is about 5 metric tons per month at Elberfeld, plus additional production at Leverkusen. Prontyl chloride (acetanilide sulfonchloride) is reacted with 2-aminethiazole solution at pH 6 to 7 in the proportion of 3 mols. chloride to 1 mol. of aminothiazole. Saponification is done with caustic soda. The aminothiazole in solution is prepared from thiourea and the methyl ether of dichloroethyl alcohol ( $\text{CH}_2\text{ClCHClOCH}_3$ ) in alkaline medium, and the neutralized solution is mixed directly with prontyl chloride. Yield is 39% based on prontyl chloride and 53% on thiourea.

Marfanil is preferred for the treatment of anaerobic infections. Recent production has been about 6 tons per month. Acetylbenzyl amine is made by reacting benzyl amine in ice with acetic anhydride, and completely distilling off the acetic acid. The product is reacted with chlorosulfonic acid to give acetylaminobenzyl sulfonchloride, which is converted to the acetylated sulfonamide with ammonia and hydrolyzed with HCl. The solubility of Marfanil in water at 37° is about 2%. The solubility of its hydrochloride is 25% or more at 37°. Such solutions are very hypertonic.

Domagk was not in the Ruhr area for interrogation, and little could be obtained from his assistants. Apparently, Domagk's group had little to do with the direction of the synthetic phases, but merely tested innumerable compounds submitted to them. Domagk develops new tests for screening and standardization. A copy of Domagk's book, "Chemotherapie bakterieller Infektionen", 1944, was obtained.

It seemed to be the consensus of the I. G. staff that Marfanil is the best compound available in Germany for the treatment of anaerobic infections. It is used largely in combinations. It seems relatively ineffective against aerobic infections, though it is adequately absorbed. No information was volunteered on comparative tests of Marfanil and Sulfadiazine (Debenal) in specific anaerobic infections. In the treatment of wounds, a 10% mixture of Marfanil and 90% Sulfanilamide was generally employed. This mixture was made at Leverkusen at the rate of about 25 metric tons per month. Were it not for a shortage of Marfanil, they would have preferred MPE, a mixture of equal parts of Marfanil, Sulfanilamide and Sulfathiazole. This formula was originally developed for the Wehrmacht. A neat plastic blower holding about 25 grams was designed. Tablets of 50% Marfanil and 50% Sulfanilamide are made for oral use, but it is understood that these were used infrequently and generally only for cases of spreading gas gangrene.

For deep wounds, there has been developed a new modified sterile mixture in bottles. It is made from a salt of 2 mols. Marfanil and 1 mol. of 1,5 naphthalene disulfonic acid. One part of this salt is mixed with 1 part sulfanilamide and 1 part sulfathiazole. The Marfanil-disulfonate salt has low solubility and acts longer than the hydrochloride of Marfanil. It is made by pouring together aqueous solutions of Marfanil. Hydrochloride and sodium naphthalene disulfonic acid, or its free acid. The salt crystallizes out. The above three-compound mixture of sulfonamides may be sterilized in the laboratory in 250 gram bottles by heating at 160° for 4 hours. In commercial practise, they may use a lower temperature for six hours. Considerable effort has been expended at Elberfeld in preparing analogs of Marfanil with improved action against aerobes. Introduction of more methylene groups (up to 6), altering the positions, and changing the sulfonamide group, as by the introduction of a phenyl group, all failed to give better compounds. New compounds were tested by Domagk against Cl. septicum infection of mice (Pararau schbrand-infektion).

Badional or sulfathiourea ( $\text{NH}_2\text{C}_6\text{H}_4\text{SO}_2\text{NHCSNH}_2$ ), is a new compound in which Elberfeld has considerable interest. This in its enol form combines with Marfanil to give a new insoluble salt. The advantage of Badional itself is its high solubility and the neutrality of its solutions. Badional has been under test about one year. It is believed to be effective against lupus of the skin, and is being tried in tuberculosis.

## Sulfones

"Tibatin" is the galactoside of p,p'-diamino-diphenyl-sulfone. Its principal advantage lies in its high solubility and neutrality, which enable highly concentrated solutions for parenteral use to be prepared. Tibatin is regarded as being of suitable toxicity and side-effects are not feared. Many other sulfones have been made, but generally they have higher toxicity.

B1034 is an experimental molecular combination of sulfapyridine and Prontosil Soluble. It was stated to have been used in Poland by Prof. Lauber in the oral treatment of Trachoma with some possible benefit.

Amidines were made experimentally, but none were found of great promise. The amidines give good tests in animals, but the results in man were disappointing. The series was not explored deeply, and apparently did not arouse very much interest.

## Biochemical and Clinical Tests

Particular inquiries were made concerning biochemical methods for the determination of Marfanil in body fluids. Since it cannot be diazotized, the common methods for sulfonamides fail. No satisfactory blood determinations have been made. It was stated that the only quantitative method found was a titration of the urine in concentrated or unconcentrated form, to determine the degree of bacterial inhibition. Dosages of Marfanil for human use were calculated empirically. Very little toxicity had been encountered and there was no evidence of renal damage or blockage, even though the compound is thought to be acetylated in the body.

Details of Kikuth's experimental work with virus and rickettsial diseases are given in Sections d. and e., and only brief mention of the sulfonamides tested will be made here. Kikuth stated that Sulfadiazine is the most active sulfonamide in the lymphogranuloma venereum group. He had tested V-147 and V-186 of Andrewes in murine typhus and was not enthusiastic about them. After experimenting since 1938 with sulfonamide aerosols and finding them unacceptable because of local irritation in the respiratory tract, he had obtained striking results in experimental broncho-pneumonitis of mice by means of a fine dust of Badional constantly stirred into the ambient atmosphere. Badional by mouth had been proved to be of no avail in clinical cases of atypical pneumonia, but no human trials of the dry aerosol had been made.

Badional is being tested for possible effect in human tuberculosis, particularly by Prof. Schulz at Leipzig. Preliminary results were stated to be encouraging, but the majority of the Elberfeld staff viewed them with skepticism. A few cases of skin tuberculosis were stated to have improved under treatment with this compound.

Processes in detail for production of Marfanil and Sulfathiazole were obtained.

#### Sulfonamide Production, I. G. Elberfeld

For this product p-amino benzene sulfone chloride is diazotised and coupled with 2-amino-7-acetyl-amino-1-oxy-naphthalene-3-6-disulfonic acid. It is used for injection but only 300 kg/mo is produced.

#### Sulfathiazole (Eleudron) Production 5 tons/mo.

##### Bill of Materials

##### For 100 kg product

55.9 kg thiourea (100% basis)  
94.9 kg dichlor ethyl methyl ether (100%)  
( $\text{CH}_2\text{ClCHClOCH}_3$ ) basis  
353 kg Prontyl chloride (acetanilid sulfone  
chloride) (100% basis)  
265-280 l. 30% caustic soda  
750-2000 kg 12.5% caustic  
440.1 sat'd salt solution  
32-35 kg glacial acetic acid  
7 kg animal charcoal  
0.15 kg sod. hydrosulfite

##### Process

##### (1) Aminothiazole

To 38 kg thiourea in 125 l. warm water (45°), 67.5 kg of the above ether is added while stirring, temperature falling to 42°, then rising to 45°; without heating, ether is added at a speed to keep at 55° during 2 hrs. Stirring is continued for 2 hrs. further and then the batch is cooled to 25° below which amino-thiazole separates out. The solution is neutralized to Congo red with 30 l. 30% NaOH.

##### (2) Coupling

The aminothiazole solution is blown to the coupling tank and diluted with 600 l. water. 240 kg prontyl chloride at 15-20° C is added

and the reaction made weakly acid to Delta paper (weakly yellow) by adding 30% NaOH. Blue litmus should test red. pH is between 6-7 and is kept so by adding NaOH during the coupling. For the first hour temperature is 20-25°C; after 3-4 hrs. it is up to 30-35° till no further NaOH is needed. Total NaOH used is 130-140 l. of 30% solution. Temperature is then held 1 hr. at 35-40° C and 1 hour at 80° C adding NaOH as needed but only 20 l. is used. The batch is made acid with 2-4 l. glacial acetic and cooled to 50°C. It is blown on to a suction filter and washed 3-4 times till the water is clear and is dried by suction. This process uses 2 mols. prontyl chloride to 1 aminothiazole with 1 mol. excess.

(3) Saponification

The batch is saponified with 5 mols. NaOH as 12.5% solution, heating 2 hrs to 103°C, cooling to 80° and blowing thru a filter press to a cooling tank. The same amount of 12.5% NaOH is added and the batch cooled to 30° C with stirring and blown on to a suction filter where it is washed twice with saturated salt solution making a paste (not a slurry) each time and putting back on the filter and washing with the salt solution. The wash solution finally must not show a dark color.

The sodium salt is dissolved in 5 pts water and treated with 5 kg animal charcoal at 60°C. It is filtered and cooled to 35°C and is bleached by adding 50-100 grams of sodium hydro-sulfite. The salt is precipitated at 30-40°C by adding glacial acetic acid to weak turbidity and then made acid by adding at once the rest of 18-20 kg acid. It is washed, neutralized and dried at 30-40° for 20-24 hrs. and then 20-24 hrs. at 70°C in a drying chamber, then sized.

1 mol. prontyl chloride is lost by saponification as well as the 1 mol. excess used.

Yields 55% of Thiourea  
25.6% on Prontyl chloride

Marfanil -  $\text{NH}_2\text{SO}_2$      $\text{CH}_2\text{NH}_2\text{HCl}$  - Production 6 tons/mo.

Bill of Materials

For 100 kg

196.4 kg acetyl benzyl amine  
from (183.8 kg benzyl amine  
(248.9 kg acetic anhydride (100% basis)

966.3 kg chlorsulfonic acid  
41.4 kg  $\text{NH}_3$  (100%) as solution  
4560 kg ice (refrigeration valve, actually br-  
ine)  
415 kg C.P HCL of 1.19 sp gr  
5.73 kg charcoal  
452 kg real ice  
661 kg absolute alcohol  
Recovered  
441 kg alcohol as 94%  
154 kg acetic (100% basis)

### Process:

#### Acetyl benzyl amine

##### Bill of Materials

###### For 100 kg

73.6 kg benzyl amine  
88.7 kg acetic anhydride  
113.7 kg ice

The benzyl amine and ice are added with stirring to the anhydride with little heat in the steam jacket. The batch is heated slowly at 100 mm vacuum recovering a 50% acetic acid. Temperature at the end of 4-6 hrs is 126°C. Test is made for free acid and if more than 1% is formed the distillation is continued after adding water until specification is reached. Product is transferred to trays, cooled, broken up and ground in a disintegrator.

#### Acetylamine-benzyl sulfone chloride

To 1000 kg chlorsulfonic acid in 1000 l. iron vessel with a stirrer on a water bath 200 kg acetyl benzyl amine are added over 6-7 hrs. keeping the temperature at 30-35°C. The reaction raises the temperature to 60°C and is held 1 hour then cooled to 20°C and blown to a 1000 l. vessel A.

In a 6000 l. vessel B lined with stoneware equipped with stirrer and lead pipes for cooling water 3500-4000 l. water and 50 kg salt are cooled to 0° to minus 3°C. From A, 4 pipes run to B dipping 25 cm. under the surface and the batch is stirred for 6-7 hrs. keeping the temperature not over 0°C. If run in too quickly, a sticky paste will be obtained and not the desired fine grain. Sampling is kept up continuously. The batch is stirred 1/4 hr., blown to suction filter and washed 3 times with 1000 l. ice water and is finally obtained as a paste.

## Acetyl Marfanil

The marfanil chloride is added to 2000 l. enameled tank with stirrer and water bath containing 150 kg 26%  $\text{NH}_3$  water and 100 l. water at temperature of 40-50°C. It is kept 1 hr. at 50°C and must always react alkaline to litmus and if not, ammonia is added, but not in excess. The batch is cooled to 20-25°, blown to suction filter, washed neutral by 600 l. water and dried by suction.

It is then transferred to a 2000 l. enameled vessel with stirrer with 750 l. water and dissolved at 95°C adding 8 kg charcoal, filtered into another enameled tank cooling with brine to 20°C. The product is blown to suction filter and washed twice with 300 l. water for each wash. Product is weighed and water content determined.

## Saponification

3 batches of acetyl Marfanil are united  
400 kg 100% product  
600 l. water including wet content of acetyl Marfanil  
350 kg 38-40% HCl  
100 l. water for washing  
350 kg 30-40% HCl for crystallizing

The 600 l. water above and the first part of the HCl are placed in a 2000 l. enameled tank equipped with stirrer and the three batches acetyl Marfanil added and heated with stirring in 3 hrs. up to the boil. It is then cooled up to 80°C, blown thru a rubber covered filter press to a 2000 l. enameled vessel equipped with brine cooling for crystallization. The first vessel is rinsed with 100 l. water which is passed thru the filter to the crystallizer to which is then added 250 kg HCl and the whole cooled to 5°C in 48 hrs. The crystals are transferred to a suction filter and the acetic is not recovered. The cake is pasted up with 600 l. alcohol and filtered. This is repeated. The alcohol is run thru the filter first without then with suction to remove the last amounts. In another 2000 l. enameled vessel with stirring the cake is treated with 1200 l. alcohol 94%, stirred 2 hrs. and allowed to stand over night with occasional stirring keeping below zero°C. The batch is filtered and the alcohol stored to be used in the first washing. The cake is dried 48 hrs. @ 80-90° C and sized.

Yield 33% on Benzyl Amine.

Sulfapyridine --- Production 3/4 tons/mo.

## Bill of materials

### Per 100 kg

355.6 kg pronyl chloride 100% (51% yield)  
263.2 kg acetanilid  
1419 kg chloresulfonic acid  
76.6 kg aminopyridine (from Degussa)  
715 kg ice  
183.2 kg caustic soda (100% basis) in solution  
126.5 kg glacial acetic acid  
12.7 kg charcoal  
318.8 kg alcohol (net)  
0.0314 kg sod. sulfite  
0.2529 kg sod. hydrosulfite

## Process

Into a 2000 l. iron vessel equipped with stirrer and brine cooling is placed 200 l. water and 500 kg ice and 350-360 kg pronyl chloride 100% is added as a 50% paste with stirring. 20 kg 30% NaOH is added to neutralize followed by 75 kg aminopyridine (100% basis).

Temperature is dropped to minus 3- 5 °C by cooling and reaction allowed to proceed till the mixture shows pH 7.5; then a thin stream of 30% NaOH is run into keep pH at 7-8 testing with Merck's Universal Indicator paper. Temperature is kept at 0°C and operation takes 6-7 hrs. As soon as no more NaOH is needed, cooling is stopped and the batch heated to 150°C for 2 hrs. A total of 120 kg 30% NaOH is used. If after 1/2 hr. no further NaOH can be absorbed, the batch is blown to a 2000 l. enameled vessel with stirring and a water bath where the temperature is raised slowly to 70°C in 2 hrs at pH 7-8 and an additional 80-90 kg NaOH 30% added if necessary. Temperature is held at 70°C for 1 hr., then cooling started and while cooling 8-10 kg glacial acetic acid is added and at 20°C the batch is blown to a suction filter and washed till the liquid is clear.

## Saponification

The batch is placed in a 2000 l. iron vessel with stirrer 800 l. water, 20 gr  $\text{Na}_2\text{SO}_3$  and 300 kg 30% NaOH and 15 kg active charcoal is added. The batch is boiled at 102-105°C and kept for 1.5 hrs., then cooled to 80°C and blown thru a filter to a 2000 l. vessel (enamel) and with a stirrer where 200 gm sodium hydrosulfite is added. While stirring, 120 - 130 gm glacial acetic is added to a weakly

acid reaction to litmus. Temperature is kept at 70° for 1 hr. to obtain proper crystal form, then brought down to 20°C, filtered and washed with water.

### Purification

The above crude sulfapyridine (60-70%) is treated in a 2000 l. enameled vessel with stirrer and water bath with 1500 kg 65% alcohol and 25 kg active charcoal for 100 kg dry weight, heating 1 hr. up to 80°C. The batch is blown to a filter and to a second 2000 l. vessel and crystallized while stirring. It is an advantage to cool quickly to 15°C to get fine crystal grain. The batch is filtered and washed with alcohol, centrifuged and dried in a chamber slowing raising temperature to 60-70°C, ground, sized and mixed.

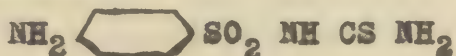
From 100 kg raw are obtained 84-86 kg sulfapyridine pure.

Yield 49.2% on 2-aminopyridine - 36.6% on Prontyl Chloride.

### Radional

#### Initial Description for Planning of Apparatus

Note: Judging by corrections in the manuscript (dated 28-10-44), the process is still somewhat incomplete).



#### Step 1 - Calcium Sulfo Compound

Materials: 75 kg calcium cyanamid (fine ground)  
50 kg 30% caustic soda solution  
100 kg Prontyl chloride (100% basis)  
140 kg common salt

Operations: 75 kg calcium cyanamid suspended in 490 l. water is stirred at 20-25° for 3 hrs. 50 kg 30% caustic soda is stirred into the filtered solution at 20-30°, followed by the molar amount of prontyl chloride calculated on the content of the calcium cyanamide solution by analysis, at such a rate that the temperature does not rise above 30°. After stirring over night 140 kg salt is added and

the batch stirred 5 hrs., filtered and dried at 30-35°.

Yield 100-105 kg or 90-95% on pronyl chloride.

### Step 2 - Sodium Sulfo Compound

Note: In the manuscript this step has been crossed out in pencil, but no substitute is given.

Materials: 53 kg anhydrous soda  
100 kg common salt  
258 kg calcium sulfo compound

Operation: 258 kg dried sulfo cyanamid calcium (above) is stirred 1 hr. in 360 l. water, 53 kg anhydrous soda is added followed by another hour's stirring with a final 1/2 hr. at 40° at which temperature it is filtered and 100 kg salt added with stirring. After cooling to 5-10° the crystals are filtered and dried well at 30-35°. Yield 260 gm = 100% of theory.

### Step 3 - Acetyl Badional MW 173

Materials: 260 kg Sodium sulfo compound  
530 kg Acetic anhydride (400 l.)  
350 cc Hydrogen peroxide 25%  
( 312 kg Sodium Sulphydrate Solution  
For H<sub>2</sub>S (260 l.)  
( 376 kg HCl Sp gr 1.09 (345 l.)

Operation: In 400 l. acetic anhydride to which 350 cc 25% peroxide has been added, 260 kg dry sodium sulfo compound is put in with cooling to 10° and simultaneous passing in of hydrogen sulfide which is continued 7-8 hrs. at 20-30° in a slow stream after all the sulfo salt is in. The cloudy solution is stirred into 1750 l. water and warmed to 40°. After 2-3 days the precipitated acetyl Badional is filtered and washed with water and dried. Yield 173 kg = 64% of theory.

### Step 4 - Saponification

Materials: 173 kg acetyl Badional

230 kg 30% caustic soda solution  
11 kg activated carbon  
382 kg 50% acetic acid  
57 kg calc. soda

Operation: 173 kg acetyl Badional is heated  $1\frac{1}{2}$  hrs. at  $80^{\circ}$  (not higher) in a solution of 230 kg (173 l.) 30% caustic soda solution and 520 l. water. After dilution with 700 l. water of  $80^{\circ}\text{C}$ . temperature 6 kg carbon is added and the whole filtered warm. Badional is precipitated by stirring in 277 kg 50% acetic acid, filtered at  $20^{\circ}$  and well washed. The filter cake is stirred up with 500 liters water and dissolved by adding 57 kg calc soda in 500 l. water and stirring 1 hr. and after addition of 5 kg. carbon is filtered and again precipitated with acetic acid. The Badional is filtered, washed, and dried 24 hrs. at  $25-30^{\circ}$ , then at  $80^{\circ}$ . Yield 55-60 kg.

Interrogated: Drs. Schönhöfer, Mietzsch, Klarer,  
Jackmann, Gottsacker, Brömmelhues,  
Lutter, Rietz, Kikuth.

## c. ANTIMALARIALS

### Production

Atebrin. Atebrin is the main compound used in the suppression and therapy of malaria. In spite of the loss of North Africa a request for 12,000 kilos per month was made by the German Government in July, 1944.

Sontochin. This new and better tolerated compound with action similar to that of Atebrin was never put on the market. Since clinical trials began in 1938, Schönhofer estimates that a total of 20 to 30 kg. of the base have been made. The synthesis is somewhat lengthy, involving 6 principal steps, and is more difficult than that of Atebrin. Ethyl propionate is converted to the ester of oxalyl propionic acid, which is condensed with m-chloraniline to give 3-methyl-4-oxy-7-(5) chloroquinoline carbonic acid ester. This is saponified to the free acid, and CO<sub>2</sub> eliminated to yield 3-methyl-4-oxy-7-chloroquinoline. The OH is replaced by Cl, and this in turn is replaced by novol diamine to give Sontochin, which is 3-methyl-4-(5'-diethyl aminopentyl-2'-amino)-7-chloroquinoline. Details of the process are given in Appendix 1.

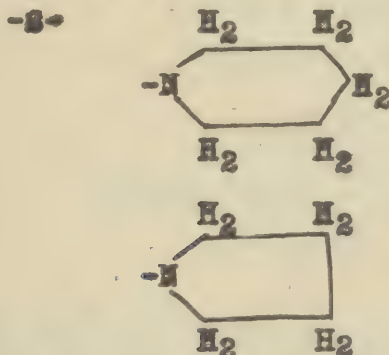
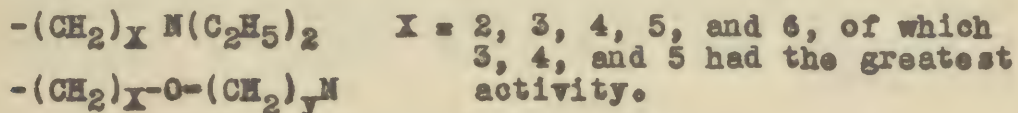
### New Chemical Syntheses

The synthesis of potential new antimalarials is carried on at Elberfeld in Schönhofer's department by a group of research chemists, each working in his own field. Schönhofer coordinates their activities, but proven workers with more than five years' experience at Elberfeld are allowed surprising liberty to follow their own ideas. New compounds are tested by Kikuth, but he takes virtually no part in suggesting new lines of chemical endeavor. Schönhofer, Andersag, Jung, Breitner, Timmler and Salzer have been the main chemists recently active in the quinoline field. Mauss, Mietzsch and Klarer have worked with acridines.

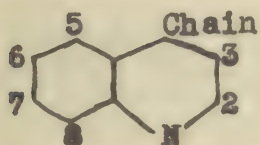
Quinolines. Andersag sketched the main lines of quinoline exploration since he came to Elberfeld in 1928 and some of the lines previously followed by Schönhofer, et al. He estimated that somewhere between 500 and 1000 quinolines had been turned over to Kikuth, of which probably only 100-150 have been developed during the war. 8-aminoquinolines were explored first but since the

making of Certuna in 1938 this work has virtually ceased. Development of 4-aminoquinolines began in the early 30s; Resochin was made in 1934 and Sontochin about 1935. Now nearly as many 4-amino as 8-amino compounds have been tried, and the side-chains and nuclear substitutions used in the Plasmochin series have been re-employed in the Sontochin analogues. However, Andersag stated that not more than 10 to 20 new 4-aminoquinolines had been prepared during the war. Part of the remainder have been 2, 3 dialkylquinolines of the Endochin type, of which at least 50 have been prepared.

In the 4-aminoquinoline series the following alterations in the side-chain were especially emphasized by Andersag:



and the following nuclear substitutions:



3- position = H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, OCH<sub>3</sub>, of which CH<sub>3</sub> was the best.  
 2- position = H, CH<sub>3</sub>, the latter having no activity.

5- position = Cl, CH<sub>3</sub>.

6- position = Cl, CH<sub>3</sub>, OCH<sub>3</sub>

7- position = Cl, Br, I, F, OCH<sub>3</sub>, SCH<sub>3</sub>, CH<sub>3</sub>, of which the Br was as active as the Cl.

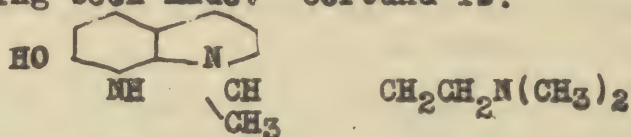
8- position = Cl, CH<sub>3</sub>.

Also the dichlor and the dimethyl analogues in the following positions: 5 and 6, 5 and 7, 5 and 8, 6 and 7, and 6 and 8.

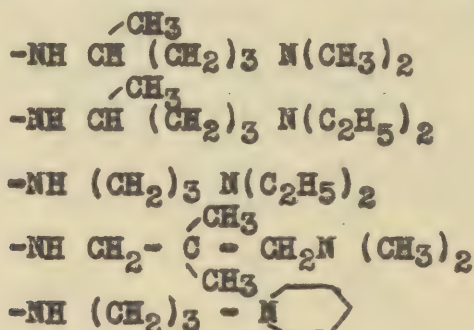
In the 8-aminoquinoline series, all the above analogues compatible with this structure were tried. In the side-chain, (CH<sub>2</sub>)<sub>x</sub>N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, x was carried out to 12. And

in the side chain,  $(\text{CH}_2)_x \text{NH}_2$ , x was carried out to 7. A nuclear substitution<sup>2</sup> of  $\text{CH}_3$  was tried in the 4 position, as well as in other locations. A 5-position methoxy compound was made. None of these analogues gave any indication of improved activity by Kikuth's tests.

Only 8 or 10 analogues of Certuna were recalled by Andersag as having been made. Certuna is:

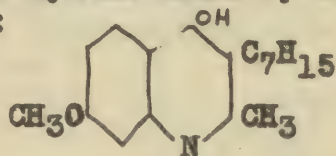


This compound is interesting in that a change to  $\text{CH}_3\text{O}$  in the 6-position greatly increases the toxicity. All of these analogues consisted of variants in the side-chain as follows:



Again these showed no special advantages by Kikuth's methods of screening. With the possible exception of the next to the last one, all these side-chains were also used on the Sontochin and the Plasmochin series.

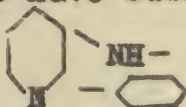
The 2, 3 dialkylquinoline series were built about Enéochin which was synthesized by Salzer about 1940 and has the structure:



In this series, the straight side-chain in the 3-position was explored all the way from  $\text{CH}_3$  to  $\text{C}_8\text{H}_{17}$  and maximal activity found from  $\text{C}_4$  through  $\text{C}_7$ . Variations of  $-(\text{CH}_2)_x \text{O}(\text{CH}_2)_y \text{CH}_3$  were also tried. As far as Andersag could remember, no amino groups were inserted because of difficulties in synthesis. Most of the common nuclear substitutions used in the aminoquinolines were tried.

In spite of technical difficulties a few isoquinolines

have been made, using side-chains developed for the plasmo-chin series, and all have been without appreciable activity. Quinoxaline-type compounds have also been explored without results. And so have substituted pyridines with the general structure:



Acridines. Mietzsch stated that about 1000 compounds of the atabrine series had been screened; but in the last 4 to 5 years no further compounds of this type have been developed.

Avian Screening. Prof. Kikuth came to Elberfeld in 1929 and eventually succeeded Roehl as head of the division that tests new compounds against tropical diseases. He is a physician, without special training in chemistry, and holds the chair of tropical medicine at Düsseldorf. In normal times he has 1 medical assistant, 1 zoological assistant, 4 to 8 technicians, and 30 to 40 female assistants, who make microscopic readings, etc. The laboratories are excellent, roomy, well kept, and well equipped.

As new compounds are received from the chemists, Kikuth assigns each a number of his own, as well as the number of the synthesizer. Formulae are kept in a master notebook so that those conducting the tests may have no preconceived notions regarding the results. On each compound a battery of 10 to 20 different tests are set up, which include virus and parasitic diseases other than malaria. An elaborate book-keeping system is used with numerical cross-references to individual protocols, and no compilation of all the work done has ever been made.

Kikuth has continued the numbering system which Roehl had carried to about 6000 in 1929, and up to the present 21,161 compounds have been tested. 200-300 of these are duplications, largely due to the need in the early years of the war of testing new batches of Atebrin for activity. Only a small proportion were designed primarily as anti-malarials, but all have been screened. Before the war an average of 20 to 30 compounds a week were run through, but this has fallen off recently to an average of only 2 a week. In the two months of April and May 1942 about 100 compounds were tested. Since then only 1700 additional ones have been completed. Part of this decrease has been due to the privations of the war and part to a decrease in the priority of investigations in tropical medicine since the loss of North Africa.

Before the war Kikuth's standard procedure for a new compound which might show antimalarial action was to try its

effect both in the treatment and in the prophylaxis of canary malaria and to assay its gametocidal action in chronic hemoproteus infections of rice-finches. Since the start of the war he has been unable to obtain rice-finches and has had to omit this assay. The supply of canaries in Germany was ample. In canaries he may use cathemerium or relictum--he believes it makes little difference. The standard Roehl procedure for blood-induced infections with oral catheter-dosing for 6 days is employed to test schizonticidal action. In the causal prophylactic test, the only modification in that infection is induced by the intramuscular injection of sporozoites obtained by dissecting out the salivary glands of infected mosquitoes. About 70 birds can be infected with the suspension obtained from 50 satisfactory mosquitoes. 4-6 birds are used for each test. Kikuth has never used lophurae or a simian strain. For a period before the war he kept a strain of gallinaceum in chicks, and he also had elongatum in canaries.

Kikuth is interested only in new compounds which show a definitely superior activity or lower toxicity than known compounds in his avian tests. If he finds such a substance, he passes it to Prof. Weese for more detailed pharmacological work than the rough canary and mouse MLDs he has obtained. Weese or Hecht test the compound in other animals and determine specific LD 50s for various routes of administration. If the toxicological results do not contraindicate, the compound may then be ready for clinical trial.

Kikuth feels that his avian screening is a satisfactory test for activity in human malaria. He admits there have been disappointments, but the method which reveals the advantages of Atebrin and Plasmochin is good enough for him. He seems not to feel that there is any less chance of correlation in prophylactic than in therapeutic results between avian and human results. He has pretty well discarded Roehl's Therapeutic Index, though he still mentions it occasionally. His canary tests begin as close as possible to the maximal tolerated dose, and results are expressed in terms of the dilution of the compound (of which 1 cc is given per 20 gm of bird) with which a certain result is produced. As far as could be determined, no one has made any particular efforts to quantitate the pharmacological testing by developing means by which to test the blood-levels of compounds.

Kikuth is a strong believer in E-forms, which to him mean Endothelial-forms. He thinks that forms of this type must be responsible for vivax relapses. He also considers

that gametocidal action has some correlation with activity against E-forms.

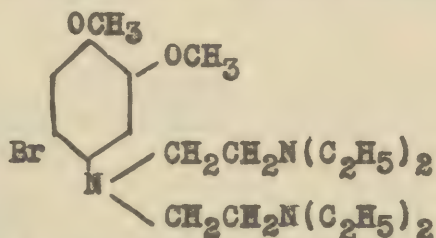
Another avian test used occasionally by Kikuth is the Exflagellation Test, in which exflagellating gametes are subjected to various concentrations of the test compound. Under these circumstances Plasmodium 1/50,000 will have a demonstrable effect within an hour.

#### Compounds found to have avian activity

Plasmodium. One of the reasons Kikuth thinks so highly of the screening against hemoprotozoans is that it enabled him to differentiate the actions of Plasmodium and Atebrin. He points out that Atebrin alone has no effect on the circulating gametocytes, that Plasmodium alone causes them to disappear only temporarily, but that Atebrin plus Plasmodium causes a permanent cure. It is his belief that plasmodium acts directly, without preliminary degradation. He bases this on (1) the speed of its demonstrable action in the Exflagellation Test, and (2) the fact that almost every conceivable modification has been tested and all show a diminution in activity.

Atebrin. This is the staple compound for quickly terminating an attack. At the time it was first being developed, the analogue without the chlorine atom also is believed to have had a clinical test.

Dimelasmin. This compound has the structure:



It was found by Kikuth in 1936 to have avian activity as follows:

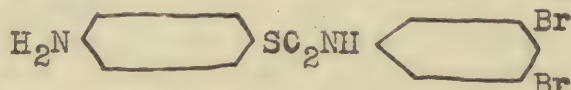
Canary Toxicity = 1/100 dead, 1/200 living.  
Blood-induced Canary Malaria = 1/200, 1/400, 1/800,  
1/1500, 1/3000, 1/6000  
and 1/12,000 Temporary  
Cure.  
1/25,000 and 1/50,000  
Slight Effect  
1/100,000 No Action

Sporoz-induced Canary Malaria = 1/400, 1/800, 1/1500  
 and 1/3000 Temporary  
 Cure  
 1/6000 Slight Effect  
 1/12,000 No action \*

\*(This summary and succeeding ones are based on the concentration of the test compound used. Thus 1/100 means 1.0 gm in 100 cc of distilled water. 1.00 cc of the given concentration is used as the dose for a 20 gm bird. For heavier or lighter birds the quantity of solution administered is altered proportionately. Temporary cure is the translation of Wirkung; Permanent Cure of Wirkung-Heilung; Slight Effect of Spur-Wirkung; and Trace of Action of geringe-Spur-Wirkung.) For standardization of this test in terms of quinine, atabrin, and plasmoquin, see page 119.

Clinical tests of Dimeplasmin both by Sioli and in Malaya showed no activity. However, in view of the marked activity in cathemerium, Kikuth is anxious that Sioli should make further tests for causal prophylactic activity.

Bemural. This compound, developed in 1937, has the structure:



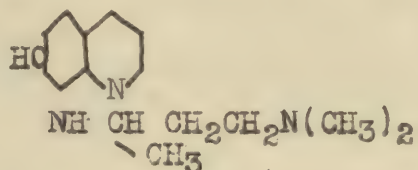
It was found to be more active than the iodine analogue which was made first. Kikuth made the statement that these are the only sulfonamides active in avian malaria. His protocol on Bemural is:

Canary Toxicity = 1/100 dead, 1/200 living  
 Blood-ind. Canary Malaria = 1/200, 1/400, and 1/800  
 Temporary Cure.  
 1/1500 Slight Effect.  
 1/3000 No Action.  
 Sporoz-ind. Canary Malaria = 1/200 and 1/400 Slight  
 Effect.  
 Hemoproteus Infection = 1/200 No Action.  
 Exflagellation Test = 1/1500 No Action.

Bemural was sent to Hamburg in 1939, but Kikuth is not sure that it was ever tested. It is the only one of the experimental I. G. antimalarials that is known to the Japanese. A letter from Prof. Ishii of Tokyo in 1941 indicated that he was interested in it but gave no clinical data.

Certuna (Cprochin, Cilional)

Certuna was produced about 1938 and has the structure:



Kikuth's protocol on it is:

Canary Toxicity = 1/800 dead, 1/1500 living.

Blood-ind. Canary Malaria = Half as active as Plasmochin.

Sporoz-ind. Canary Malaria = 1/1500 No action.

Hemoproteus Infection = 4 times as active as Plasmochin.

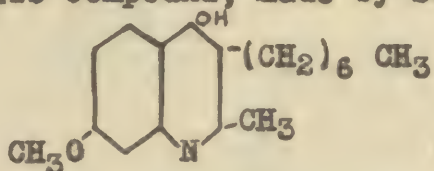
Exflagellation Test = About 1/200,000 Temporary Cure.



are Sontochin-M (the methylene bishydroxynaphthoate) and Sontochin-R (resorcin carbamate). Dosage, contrary to the practice in Plasmochin, is always expressed in terms of Sontochin base.

Sioli tested various salts of Sontochin in 1938-9 and found them active in the termination of blood-induced vivax malaria in doses as low as 0.3 gm daily. He encountered absolutely no toxic symptoms. Further trials of this compound will be detailed below under "Further Testing of Sontochin, etc."

Endochin. This compound, made by Salzer in 1940, has the structure:



Kikuth's protocol describes its activity as follows:

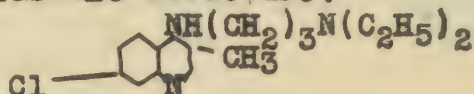
Canary Toxicity = In oil : 1/50 living.  
 Blood-ind. Canary Malaria = 1/50 and 1/100  
     Temporary Cure.  
     1/200, 1/400 and 1/800  
     Permanent Cure.  
     1/1500, 1/300 and  
     1/6000 Slight Effect.  
     1/12000 Trace of  
     Action to No Action.  
     1/25,000 No Action.  
 Sporoz-ind. Canary Malaria = 1/100 and 1/200  
     Temporary Cure.  
     In oil: 1/400  
     Temporary Cure.  
     1/800 and 1/1500  
     Slight Effect.  
     1/3000 No Action.  
 Hemoproteus Infection = No tests made.  
 Exflagellation Test = 1/3000 and 1/6000 Temporary  
     Cure. 1/12,000 No Action.

The activity of Endochin in cathemerium and relictum is such that a single dose given 1 hour after a blood-induced infection will give a Permanent Cure. Kikuth, therefore, had high hopes for it in humans.

In 1941 Sioli tested Endochin in the treatment of 7 cases of blood-induced B.T. malaria. Doses up to 0.4 gm

tid for 6 days were used without effect, and one case developed albuminuria. 3 cases were given 0.1 gm tid as a test of causal prophylaxis, starting the day before being bitten by infected mosquitoes. Two received this regime for 7 days and yet developed malaria. The third was still receiving 0.1 gm tid on the fourteenth day when his malaria attack began. Protocols of these experiments are given in Appendices 3 and 4. It was planned that Sioli was to test another salt, called Endochin A, but this seems never to have been done. A sample of Endochin was obtained.

Brachysan. This compound, synthesized by Andersag and Breitner in 1943, has the structure:



Kikuth's protocol on it is:

Canary Toxicity = 1/50 dead, 1/100 living (barely)  
 Blood-ind. Canary Malaria = 1/100 dead, 1/200,  
 1/400 and 1/800  
 Temporary Cure.  
 1/1500 and 1/3000  
 Slight Effect.

2nd trial of Blood-  
 ind. Canary Malaria = 1/100, 1/200, 1/400  
 and 1/800 Temporary Cure.  
 1/300 No Action.  
 Another 1/3000 Slight  
 Effect.

Sporoz-ind. Canary Malaria = 1/200 No Action.  
 Hemoproteus Infection = 1/200 No Action.

Sioli tested Brachysan in 1944 and found it about as active as Sontochin. He cured blood-induced tertian malaria with 0.1 gm tid for 7 days and abolished fever and parasites temporarily with 0.3-0.5 gm on 2 successive days. His protocol is given in Appendix 4.

Sioli's Methods of Clinical Testing. Since the days of Roehl, compounds of promise have usually gone first to F. Sioli, Prof. of Psychiatry at Düsseldorf, for clinical trial. Sioli is in charge of the 900 bed Heil- und Pflgeanstalt at Düsseldorf-Grafenberg and before the war had an average of 10 cases at a time on induced malaria. Recently he has had fewer appropriate cases, and his present average of two makes it difficult to keep his malaria

strain going. Originally he had B.T. derived from Wagner-Jauregg, but since the war he has used only the Madagascar strain obtained from Horton. In 1933 Sioli established an insectarium modelled on that at Horton. He uses *A. maculipennis* caught along the lower Rhine.

Sioli looks like a family doctor of the old school. When he was visited, in company with Kikuth, he said he couldn't remember details, and had to rummage out papers and charts from a series of untidy folders. It appeared that some of his older records had been lost and that Kikuth always makes a personal check of the results before accepting them.

Sioli starts with dosages recommended by Kikuth for the termination of blood-induced BT malaria. His follow-ups are often 2 weeks or less. He is interested in doses which will give a cure of this duration. Having determined these, he then works out the minimal dose which has any effect. He may work with a new compound for 6 to 12 months before sending a report to Kikuth. It seems unlikely that he has tested many more than 12 compounds in the last 15 years.

Though proud of his insectarium, Sioli uses mosquito-induced malaria very rarely. Kikuth has had difficulty getting him to design proper tests for causal prophylaxis. His protocol for Endochin seems to be one of his better efforts. It is based on 5 patients, one of whom served as control.

#### Further Testing of Sontochin and Brachysan.

Sontochin. Although Sontochin is not a causal prophylactic, Kikuth considers it to be better than Atebrin as a suppressive prophylactic. Schönhöfer has tried to develop new derivatives of Sontochin which would be effective against the endothelial phase; these gave promising results in canaries, but failed in man.

A manuscript from Elberfeld dated Dec. 29, 1937 (Appendix 5) summarizes the work done on Sontochin before it was given to Sioli. Pharmacological studies showed LD50s for acute toxicity as follows: Subcutaneously = mouse 100 mg/kg, rabbit 100-125 mg/kg, and cat 50-75 mg/kg; orally = rabbit 200-300 mg/kg, guinea pig 300-500 mg/kg, and cat 50-75 mg/kg; intravenously = rabbit 20-25 mg/kg. MLDs for daily oral administration for 30 days were guinea pig 500 mg/kg, cat 250 mg/kg, and rabbit 250 mg/kg, showing there

was only a slight cumulative effect. Permanent cure of chronic hemoproteus infection had been achieved by means of Plasmochin 1/6000 for 4 days followed by Sontochin 1/200 for 4 days. This indicated that the action of Sontochin was similar to that of Atebrin.

Another manuscript, written in retrospect by Kikuth (Appendix 6), gives further details of the comparative action of Sontochin and Atebrin. It mentions that Sontochin was inactive in the Exflagellation Test.

After Sontochin was reported by Sioli as being active in the termination of B.T. attacks, it was sent in 1938-9 to Prof. Mühlens of the Hamburg Tropeninstitut. A manuscript (Appendix 7) by Menk, who worked with Mühlens, describes the success achieved with it in both B.T. and M.T. early in 1939, and also in some 65 cases in Cameroon. In the latter series it was at times used intravenously in doses of 0.2 gm of a 5% solution put up in sterile ampoules. There were no significant symptoms of CNS toxicity, though occasionally there was mild lowering of the blood pressure. Steinbömer found that 0.4 gm given intramuscularly at one time might cause vertigo and vomiting, so 0.3 gm was recommended initially by this route for advanced cases, especially of M.T. Dosages of 0.5 - 0.6 gm for 7 days were generally advised, and for oral use Sontochin-R tablets were preferred to Sontochin-M because although bitter to the taste they were absorbed more rapidly.

104 cases are mentioned by Menk as having received simultaneous treatment with Plasmochin and Sontochin. 0.015 to 0.02 gm of Plasmochin daily was found to be well tolerated for 5-7 days in conjunction with 0.3 to 0.6 gm of Sontochin. No details are given as to relapses after this treatment except for the statement that they did occur, even after higher doses.

Two manuscripts by Menk and Steinbömer (Appendices 8 and 9) describe experimental trials of Sontochin suppression. The first, dated November 15, 1942, states that 0.05 gm daily of Sontochin-M failed to prevent the breakthrough of malaria, after repeated bitings of B.T. and M.T. infected mosquitoes, in 3 of 10 cases, but that 0.1 gm daily remained completely effective in 8 cases after observations lasting 3 to 16 months. The second manuscript (undated) adds that suppression was still complete in 7 cases that had continued therapy for nearly 2 years. It also mentions that the bombing of Hamburg destroyed the mosquito colony of the Institut and greatly curtailed the

work. Two cases on suppression with 0.1 gm of Sontochin-M, however, were noted 9 and 10 days respectively after very heavy infections to develop transient fever without detectable parasitemia.

In 1942 Dr. Hauer in Berlin and Prof. Fischer in Munich were asked by the Surgeon General's Office of the German Army to try out Sontochin. Dr. Rose, Chief Consultant in Tropical Medicine to the Luftwaffe also made a large scale trial. Finally Prof. Schulemann of Bonn and Dr. Sager of Leipzig were drawn into the circle. The Pasteur Institute of Algiers conducted some field trials, and a test of suppression was commenced in the Bulgarian Army, but proved unsatisfactory due to poor discipline. In all about 4000 cases have been treated.

Papers on Sontochin were prepared for publication by Kikuth, Mühlens, and Menk, of which the manuscripts cited are samples, and Sioli was asked to submit one. Publication, however, was held up by Hoerlein, apparently not out of fear of aiding the Allies but because he considered that the advantages of Sontochin over Atebrin were not sufficient to justify, till after the war, any publicity which might force Elberfeld to switch its manufacture from Atebrin to a compound that was more difficult to synthesize. Kikuth is positive that no word concerning Sontochin was sent directly to the Japanese, but he says that Dr. Rose spoke freely about the compound while lecturing in Turkey in 1943 and so incurred the displeasure of the I.G.

Brachysan. After Sioli reported in December 1944 that Brachysan was as effective as Sontochin in terminating induced malaria, some of the compound was sent to Dr. Rose. Latest advices indicate, however, that larger doses are required to terminate an attack and that even so the disappearance of parasites is slower. Kikuth estimates that Brachysan is about 80% as active as Sontochin, but its greater ease of manufacture is such that I. G. is still considering its commercial production. It is said to be as non-toxic as Sontochin. No causal prophylaxis tests with it in man are known to have been done, but it is not expected that it would have any action different from that of Sontochin.

Chinoplasmin. Kikuth stated emphatically that the combination of quinine and Plasmochin was more efficacious than Atebrin in terminating the chronic relapsing case of B.T. He quoted statistics to indicate that a relapse rate with Mediterranean strains of about 50% after Atebrin could

be reduced to 5% by this combined treatment. For this purpose he recommends 3-4 tablets daily of Chinoplasmin, each consisting of 0.3 gm of quinine Sulfate and 0.01 gm of Plasmochin. The full course lasts 2-3 weeks, but a shorter one of 7 days duration is sometimes given for mild cases. The teachings of Kikuth and Menk are contained in the 1944 edition of the book by them, entitled "Die Chemotherapie der Malaria".

#### d. Remedies for Tropical Diseases.

General Remarks. Chemotherapy of tropical diseases was studied in Kikuth's laboratory in a manner similar to that employed in virus and rickettsial diseases. New compounds when available in sufficient quantities were tested for their effect on the diseases listed below.

##### Diseases:

Trypanosomiasis  
Leishmaniasis  
Schistosomiasis  
Amoebiasis  
Bartonellosis  
Leprosy  
Piroplasmosis

##### Test Animals:

Mouse  
Hamster and culture  
Mouse  
Kitten and culture  
Rats  
Rats  
Dogs

In brief, there have been few if any encouraging new developments at Elberfeld in the chemotherapy of tropical diseases during recent years. Indeed the 6th edition of Stitts, Diagnosis, Prevention and Treatment of Tropical Diseases published in 1943 contains complete discussions of practically all the newer drugs mentioned by German workers except Acaprin which was discovered in 1935 and has been employed in veterinary practice for piroplasmosis. Interest in tropical diseases and investigation dealing with their chemotherapy declined preceptably after the war started and especially after the Allies reconquered Africa.

##### Trypanosomiasis.

(a) African Sleeping Sickness. Bayer 205 (Germanin) is still considered the drug of choice for prophylaxis and for treatment. Antimony preparations, particularly Fouadin used along with Bayer 205 are thought to be of value in the more chronic cases, Kikuth emphasises the not infrequent development of arsenic-fast strains of Trypanosoma gambiense in patients inadequately treated with the drug. Although Germanin-fast strains of Trypanosoma gambiense have been encountered in the laboratory they have not been recognized in the field.

(b) Chagas Disease. Little work seems to have been done on Trypanosoma cruzi at Elberfeld. Drugs of the Surfen series including Congasin and #7602 have been studied by Prof. Fussgänger of I.G. Höchst and a discussion is given in the report on that target.

(3) Leishmaniasis. Kikuth and Schmidt are of the opinion that Solustibosan is the most useful member of the pentavalent antimony compounds in the treatment of Leishmania infections in man and animals. In addition to the work mentioned in Stitt's 6th edition, Kikuth and Schmidt have reported on further studies on the experimental infection in hamsters and have revised the use of Solustibosan in patients with this protozoal disease in Spain in 1942 and 1943. Solustibosan has been packaged in two new forms, (1) a more concentrated aqueous solution containing 100 mg of Sb per cc and (2) a suspension of the drug in oil with 54 mg of Sb per cc. The Spanish cases were treated intramuscularly with one or the other of these new preparations.

(4) Schistosomiasis. The Elberfeld workers consider the trivalent antimony preparation Fouadin (Neoantimosan) to be the drug of choice for treatment of infections caused by Schistosoma haematobium and S. mansoni. However, they have had little first hand information on the treatment of schistosomiasis since the war began.

Although Kikuth has published nothing on experimental infections with Schistosoma he has worked consistently with this group of agents for a number of years. Therapeutic effects of test drugs are studied in mice, and occasionally monkeys and rabbits infected with Schistosoma mansoni maintained in the South American snail guadalupensis and in mice (?) infected with Schistosoma Haematobium maintained in Egyptian snails.

(5) Filariasis. No encouraging development in the chemotherapy of filarial diseases was reported by the German workers. Prof. Hans (Antimony) Schmidt still favors the use of Fouadin in oil for Filaria bancrofti. A more recent trivalent antimony preparation, designated as 779, was sent to tropical China just before the war. No reports of its usefulness in filariasis have been received. The formula and method of preparation of 779 are given in Appendix II.

(6) Amoebiasis. A fairly recent compound prepared in the I.G. laboratories has been reported to be of value in the treatment. An article dealing with this compound was published by A. Nauer. "Erfahrungen mit einem neuen Mittel gegen Ruhr-Amöben-Infektion", Deutsche Tropenmed. Zeits. 1943, 47, 153-161. The compound, which is designated "Präparat 9659a", or WIA, is an arsenic acid-bismuth combination containing 15.7% arsenic and 37.0% bismuth. It is dispensed in 0.25 mg tablets. According to Nauer's paper, the production of this drug on a large scale was not possible in 1943; no sample was available to CIOS team 110. The drug is considered to be essentially non-toxic, since rabbits tolerated 2.0 gm per kilo of body weight. Kittens with amoebic dysentery were treated with 1 or 2 doses daily of 30 mg of WIA per kilo body weight, with the result that the majority were entirely freed of E. histolytica while the remainder showed a marked reduction in amoebae. Pathological study of the latter showed that they had deep seated ulcerative lesions of the gut.

The drug was tried on several scores of patients with amoebic dysentery. The author summarizes his clinical results as follows.

"1. The arsenic acid-bismuth preparation No. 9659a (WIA) was invariably tolerated well; toxic symptoms were never encountered. The new substance does not have a laxative effect, indeed, in many cases of chronic enteritis it stopped the diarrhea rapidly and permanently.

2. In all cases of latent amoebiasis (direct translation-avirulent infection) a rapid and apparently permanent disappearance of the minute forms and cysts was attained. In most cases this effect was produced within the first few days of beginning treatment.

3. Clinical amoebic dysentery, with active pathogenic forms of E. histolytica was not influenced by WIA. Neither the subjective symptoms nor the objective signs (proctoscopy) were improved or eliminated after oral or rectal administration of WIA. In all these cases Yatren-Emetin therapy was applied and the usual beneficial effect attained.

4. The effect of WIA on non-pathogenic intestinal protozoa is also striking.

5. In summary, in the WIA preparation we have according to all indications a new excellent remedy to eliminate the so called avirulent infection with E. histolytica. It appears especially well suited for prophylaxis and therapy, both in individuals and in large groups. It is as effective as Yatren on E. histolytica and is tolerated much better. Its antidiarrheal and sedative effect upon intestinal peristalsis is remarkable."

(7) Bartonellosis. Kikuth has worked extensively over a period of years with Bartonella infection of rats. The best chemotherapeutic agent that he is aware of for this experimental disease is still the arsenic-antimony compound which was designated 386B, early in the last decade. Kikuth's original observations on the efficacy of this compound in the animal infection have been confirmed by himself and others. The first glowing accounts of the beneficial effect of this drug in Carrion's Disease (Mamrigne, Reforma Medica (Peru) 1937, 23, 661) were subsequently dampened by reports of other Peruvian physicians, see Stitt's 6th Edition. Because of the action of 386B on at least one member of the Bartonella group, the formula and method of preparation of the compound were obtained. They are given in the Appendix 12.

(8) Piroplasmosis. A quinoline derivative known as Acaprin with the formula N.N' (Bismethylchinolylum-methylsulfat-6-) urea was reported by Kikuth in 1935 to be active against piroplasmosis. Kikuth has subsequently continued to study the chemotherapeutic effect of this drug ("Die Behandlung der Piroplasmosen mit Acaprin", Deutsche Tierärztliche Wochenschrift, 1941, 16, 190-192). This paper contains a summary of the results obtained with the drug in different types of piroplasma infections. Good results are reported in its use against

Babesidae canis, (B. bigemina, B. argentina, B. bovis, B. Berberg, B. caballi, B. equi and B. trautmanni. Some beneficial effects are recorded against B. divergens, B. ovis, Theileridae dispar and Th. mutans. Kikuth says that the general use of this drug has not been great because the war cut off most of the potential markets. It has been prescribed extensively, however, in the Balkans. He also states that in cattle the spread between the therapeutic dose and the toxic dose is not great.

## e. Remedies for Virus and Rickettsial Diseases.

### General Remarks.

In accordance with the general plan employed in I.G. laboratories which are interested in chemotherapy each new chemical substance is tested routinely for its effect on a number of experimental infections. After toxicity tests on mice and canaries have indicated the usable dosage of a new drug, it is studied in Prof. Kikuth's laboratory for its therapeutic action in animals infected as follows.

<u>Virus</u>	<u>Animals</u>	<u>Route of Infection</u>
Influenza A	Mouse	Intranasally
Lymphogranuloma Venereum	"	Intracerebrally
Bronchopneumonia of mice	"	Intranasally
(Psittacosis-Lymphogranuloma group)		
Lymphocytic Choriomeningitis	"	Intracerebrally
Murine Typhus	"	Intraperitoneally (some
Avian Pox, Canary type	Canary	Cutaneously intra-
Ectromelia	Mouse	" nasally)
Infectious Myxomatosis	Rabbit	Intracutaneously

Until several years ago 50-100 new compounds were received and tested each week in Prof. Kikuth's laboratory. The number then gradually diminished to 10-20 weekly. The shortage of animals, which has been developing progressively since the war started, became so acute in the fall of 1944, that most of the chemotherapeutic work had to be discontinued.

The more promising results during the past few years in these studies are summarized in the following sections.

### Typhus Fever

Relatively few precautions, other than vaccination are taken to protect the workers engaged in studies in experimental murine typhus. Since the intranasal route of inoculation is sometimes used, it is not surprising that practically all of the workers have developed typhus. No deaths occurred among the eleven persons who became ill from laboratory infections. Experimental work on epidemic typhus is not done in Kikuth's laboratory because of the danger of infecting the workers. Strains of the rickettsiae of Spotted Fever, Boutonneuse and Scrub Typhus have not been available.

No beneficial effects were obtained with the ordinary sulfa drugs in mice experimentally infected with murine typhus; thus, the experience of Kikuth agrees with that of workers elsewhere. Although several German publications claimed that sulfa drugs favorably influenced the course of typhus fever in human beings, Kikuth says he has examined the protocols of the authors and that the data was inadequate to support such conclusions.

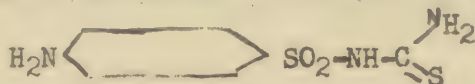
Kikuth's group prepared the compounds V-147 and V-186 which Andrews and his co-workers found effective in treatment of experimental epidemic typhus in mice. Their opinion on the efficacy of these drugs in experimental typhus is less enthusiastic than that of the British workers.

Kikuth has reported recently on the treatment of typhus with methylene blue ("Chemotherapeutische Versuche beim Fleckfieber (R. Mooseri) mit Methylenblau" (Kikuth, W., and Schilling, I), Zentrabl. f. Bakt., Parasitol. u. Infektionskr. I. 1944. 151. 293-302). The data presented are convincing. Approximately half the mice which were given a single dose of 1/1500th gm of methylene blue subcutaneously or 1/400th gm orally at the time they were infected with murine typhus survived for ten days. In contrast about 90% of the untreated control mice died from typhus before the tenth day. It will be noted that the summary of this paper contains the following statement. "Part of the treated animals eventually died from generalized infection or from the toxic effects of the drug which were manifested as an anemia". Kikuth stated in conversation that from 80 to 90% of the treated animals eventually died from one or the other causes. He also said that the drug had been tried in about 20 persons with typhus fever with discouraging results, i.e., either no therapeutic effect occurred or, in cases in which the drug was pushed, toxic manifestations developed from the drug. His opinion is that methylene blue is of importance in typhus therapy only because it gives a lead for further work.

#### Bronchopneumonia of Mice.

This spontaneous pulmonary disease of mice is caused by a virus of the elementary body group and was originally described in Kikuth's laboratory in 1941. It is undoubtedly the same disease that Clara Vigg encountered about the same time in the USA. Vigg subsequently demonstrated that the agent belonged to the psittacosis-lymphogranuloma family of viruses. Sulfadiazine is effective against this disease just as it is against lymphogranuloma venereum infection in mice. Thus, Kikuth's experience agrees with that of the American workers.

A new sulfa drug given by an unusual route has been employed by Kikuth in the treatment of bronchopneumonia of mice with highly interesting results. Badional, or sulfathiocarbonide has the following formula.



Infected mice were placed in an atmosphere containing known amounts of Badional dust. Concentrations of drug varying from 1 to 10 mg per litre of air were employed and animals were given 1 to 5 treatments of 30 minutes duration on consecutive days, the first inhalation was begun shortly after infection with the virus. Almost 100% of the infected animals survived when 5 treatments with 10/mg/litre were administered,

while close to 100% of the treated control animals died. The disease was not influenced in mice treated with a single inhalation of 10 mg/litre and only moderately influenced in mice treated with a single inhalation. of 10mg/litre and only moderately influenced when three inhalations were given. The concentration of drug in lung tissue of mice reached 5.5 mg % immediately after a 30 minute period of inhaling air containing 10mg/litre: the lung concentration declined progressively to about 1mg % six hours after treatment was stopped. The blood level of Bardional was about 2mg % at the end of the inhalation but rose to 3.5mg % an hour later, then declined to 0.5mg % at 6 hours: thus the blood concentration was always less than that of the lung tissue.

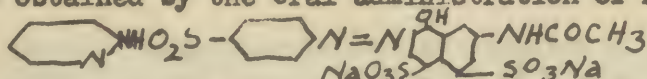
Similar experiments with other sulfa drugs have given unsatisfactory results. Too much irritation of the respiratory mucosa was produced by amounts of these drugs which might be expected to have a therapeutic effect. Kikuth attributes the successful use of Bardional to the fact that this drug gives a neutral reaction when dissolved in body fluids where as the other sulfa drugs give a strongly alkaline reaction, around pH 10.

Bardional by inhalation has not been tried in human beings. Kikuth was anxious to test its effect on a typical pneumonia, which he erroneously assumed was generally caused by a member of the psittacosis group of viruses. A clinical trial of the drug and method is undoubtedly warranted in human psittacosis and should be considered for study on a typical pneumonia of unknown etiology.

#### Other Virus Diseases.

The extensive chemotherapeutic studies carried out in Kikuth's laboratory have brought to light relatively little beyond the findings mentioned above. It may be noted that Kikuth, like several other German virus investigators, worked with Influenza A but never isolated or received Influenza B virus. It is also of interest that German investigators and clinicians are almost unaware of the disease that we call primary atypical pneumonia. Kikuth believes that they generally have failed to look for it, since one of his clinical associates in Vienna a few months ago collected a number of cases without difficulty.

A new sulfa compound was being used in the treatment of trachoma in human beings in Cracow by Prof. Lauber. Some beneficial results are said to have been obtained by the oral administration of B-1034 which is



Kikuth who was associated with the work, followed the hypothesis that large amounts of sulfa drugs should be given continuously for several weeks. The ordinary sulfa compounds were too toxic for use in this manner, but B-1034 is supposed to be sufficiently non-toxic for the purpose.

Informant - Prof. Kikuth.

## f. ANESTHETICS

Anesthetics, General and Local, have from the beginning been important subjects of study and promotion by the I. G., and the firm has contributed much to this field. The Elberfeld plant manufactures Evipal, Avertin, and Tutocaine. The I. G. plant at Hoechst manufactures Benzocaine ("Anesthesin"), Novocaine, Pantocain, and Solaesthin (methylene chloride). No anesthetics, so far as known, are manufactured at Leverkusen.

General Anesthetics and Basal Narcotics at Elberfeld include Evipan and Avertin. The work on the Evipan series was completed in 1932. Evipan is supplied as the sodium salt in powder form in ampoules of 0.5 and 1.0 gram. It was accepted by the Wehrmacht as the standard intravenous anesthetic agent (although they also used some "Eunarcon" supplied by Riedel-de Haen, which Weese regards as unsafe because of its large content of antipyrine as a solubilizing agent).

Evipan Sodium is used (a) intravenously as a 10% solution containing 1 gram, given in a single dose for operations of short duration; (b) intravenously in 2% to 10% solutions, intermittently injected, for operations of long duration; (c) by the drip method simultaneously with normal saline; (d) 10% solution intramuscularly. This was said by Weese to produce light narcosis of long duration. He stated that there was no necrosis of tissue when this technique was employed. Dr. Schellenberg, in charge of pharmaceutical manufacturing at Leverkusen, stated that the schedule called for 300 to 400 thousand ampoules per month, but not even half this amount was ever actually produced. For example, in June, 1943, a fairly typical month, 16,000 0.5-gram ampoules and 198,000 1-gram ampoules were finished.

A thiobarbiturate, "Narkogen", was also studied for these purposes in 2000 to 3000 cases. The results were too variable and convulsions occurred too frequently.

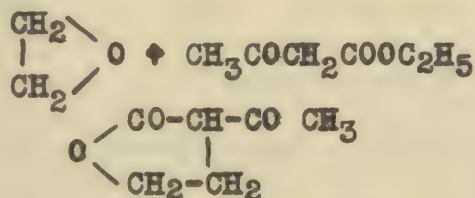
Weese stated that Evipan is widely used and he considered it "good enough". They have not done further work in this field since 1933.

Avertin is no longer considered important as a general anesthetic. Apparently interest in it as a basal narcotic has also lagged. The dose is 100 mg. per kilo body weight, with supplemental ether or Evipan. Weese did not favor these combinations, but offered no definite reasons for his position. Avertin is also used in doses up to 100 mg. per kilo for the control of tetanus convulsions.

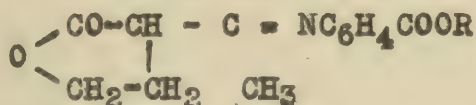
Of the local anesthetics, Tutocaine is no longer manufactured but reserve stocks are being sold. It was made from an intermediate product resulting from the synthetic rubber work at Leverkusen. The therapeutic index is too low. A much better product is Pantocaine (made at Hoechst), which is the spinal anesthetic of choice in Germany. They use a 0.1% solution in saline for local infiltration, a much higher concentration than employed by the British. The Germans use 0.5% to 2% for topical application.

The local anesthetic cartridges, "Carpules" are manufactured at Leverkusen. Their production rate was 1 to 2 million per month. If good gum rubber stoppers were used, the solutions kept a year. With later Buna compositions, the stability was not good, and deterioration was evident in 6 months. They employ chlorbutanol as a preservative, but use no nitrogen or hydrogen protection.

Dr. Schönhofer stated that they are not now working on local anesthetics or vaso-constrictors. They made a new product, hoping for combined local anesthetic and vaso-constrictor effect, but so far as could be learned, no favorable results have been obtained. It was made as follows:



The above is condensed with anesthesin to give



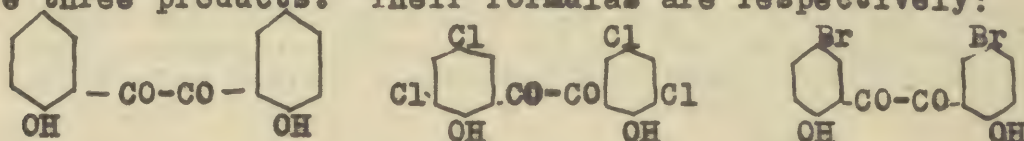
## g. ANTIBACTERIAL AGENTS

### Penicillin and Dibromosalicil.

Before the war, the Elberfeld laboratories tested about 2000 compounds per year against bacterial infections.

The Penicillin work at Elberfeld has not passed beyond the early research stage. They tried several hundred strains of *Penicillium notatum* and other molds, none of which yielded anything better than Penicillin. For the latter, most of research was done in Erlenmeyer flasks, in two rooms each about 20 feet square. More recently they have been working on submerged culture methods, using bottles of approximately 8-liter capacity. They stated that they obtained a product of about 200 Oxford units per milligram, but they have not recently pushed this work.

Salicil, Tetrachlorosalicil, and Dibromosalicil. Prof. Richard Kuhn is apparently responsible for the interest in these three products. Their formulas are respectively:



The I.G. Elberfeld were requested to make larger quantities of these, which they did. Interest in Salicil was lost because of effectiveness; the tetrachlorosalicil was found to be rather highly toxic; the dibromosalicil was studied in more detail. Several kilos were made.

Weese carried on the toxicological work, and found that the dibromo compound should be tolerated by man in 10-gram doses. Professor Hörlein, Director of the Elberfeld company, stated that the results of tests with dibromosalicil had been disappointing, and they had little further interest, in that compound. In substantiation, he submitted letters and reports which are summarized as follows (the dibromo compound is given the Elberfeld code No. Q335, and the Corresponding diiodo compound No. Q336):

Data submitted by Prof. Domagk to Prof. Kuhn in letter 7 March 1944 -- Tests on growth of Tb bacilli using the egg media of Hohn (a) as usual with  $Mg SO_4$  (b) without  $MgSO_4$ .

Times in which control tubes showed strong growth (+++) were:

	1:1000	1:5000	1:10,000	1:25,000	1:50,000	1:100,000
Q 335 a)	+++	+++	+++	+++	+++	+++
Kuhn b)	+++	+++	+++	+++	+++	+++
Q 336 a)	+++	+++	+++	+++	+++	+++
Kuhn b)	+++	+++	+++	+++	+++	+++
Sulfa-a)	0	0	0	0	0	0
thia- b)	0	0	0	0	0	0
zole						

Note by Dr. Demagk, - "also the tetrabromoisatin (our Code No. Q372) synthesized by Dr. Mietzsch showed no activity even at 1:1000 against tubercle bacilli of the human type."

On 23 June 1944, Demagk wrote to Hürlein stating the following (translation): "5,5' - Dibrom-2,2'-dioxybenzil, supplied by Prof. Kuhn, was tested under our experimental number Q335 and Prof. Kuhn was advised that in vitro the preparation shows good inhibition against staphylococci. The effect against tubercle bacilli observed by Prof. Kuhn was not substantiated, even in concentrations of 1:1000 it showed in comparison with sulfathiazole no activity against tubercle bacilli. Prof. Kuhn was informed in detail on 7 March 1944 regarding the technique used and the results obtained. In tuberculosis infected animals (typ. bovine as well as typ. human) the compound showed no activity, by either subcutaneous, oral, or local application. For further experimentation against staphylococci, we used a new sample from Prof. Kuhn, as the supply of material had been used up in the tuberculosis experiments. On 2 June 1944 we received from Dr. Linsert a new sample labeled 5,5'-Dibromsalicil. Added as a suspension to agar plates, it showed complete inhibition up to 1:50,000 against seeded staphylococci (1 drop 1:1000 diluted 24-hour culture). Sulfathiazole in the same experiment gave inhibition up to 1:250,000 (test on 21 June). With lower inoculations, inhibition can be obtained up to 1:100,000. An aqueous solution supplied by Dr. Linsert under the code Lst. 1125 (our number R 314) in an experiment on 21 June (calculated as substance 1 cc = 0.1 gram dibromsalicil per 1 cc) showed inhibition of staphylococci, and complete inhibition up to 1:30,000. The inhibitory effect against staphylococci on plates is exceeded by the following sulfonamide: Sulfathiazole; Globucid is equal in activity."

#### "Rat Studies of 7 June 1944"

"Back muscle wounds infected with staphylococci. Local treatment of 2 animals, 50, 100, and 150 mg.

	No. of Animals	Survival in 24 hrs.	Survival in 48 hrs.	Survival after 8 days
Controls	12	4	2	2
Marfanil	6	5	5	5
Debenal (Sulfadiazine)	6	6	6	6
Eleudron (Sulfathiazole)	6	5	4	4
Globucid	6	4	3	3
R314 = Dibromsalicil in solution (1cc = 0.1g)	6	4	4	4
R318 = Dibromsalicil	6	2	2	2

Hence Dibromsalicil used locally in staphylococci experiments in rats is less active than the sulfonamides Marfanil, Debenal, and Eleudron; in soluble form, applied locally, it can equal the activity of these substances when applied locally.

"Rat Experiments of 16 June 1944"

	No. of Animals	Survival in 24 hrs.	Survival in 48 hrs.	Survival after 8 days
Controls	12	2	1	1
Sulfathiazole	20	9	8	8
Globucid	20	9	9	9
R89 = Marfanil	20	10	10	10
Marfanil B				
Sulfathiazole				
Sulfanilamide				
in equal parts				
R90 = Marfanil	20	16	16	15
Marfanil B				
Sulfathiazole				
Prontosil Rubrum				
in equal parts				
R318 Dibromsalicil	20	11	11	11

Doses given to 4 animals 25, 50, 100, 150, and 200 mg. locally.

Summary: On the basis of the experimental findings an investigation of the local use, as well as the oral use, of 5,5'-Dibromsalicil (R318) is indicated, since the compound has been shown by pharmacological tests to be as non-toxic as sulfathiazole.

Toxicity of Tetrachlorsalicil - W.3214

This compound is said to have a bacteriostatic action similar to dibromdioxybenzil (-W.3065). Therefore, it was tested by similar methods toxicologically and pharmacologically.

Tetrachlorsalicil is an intensively yellow substance with an odor like that of iodoform. It is insoluble in water, but in sodium bicarbonate and in sodium carbonate with slight foaming it is quite soluble. In mice, the oral m.l.d. of the powder suspended in tragacanth is 75 mg/kg. Therefore, tetrachlorsalicil is at least 12 times as toxic as dibromdioxybenzil. This higher toxicity seems to be due to its greater absorbability, since the powder dissolved in alkali given intravenously to mice has an m.l.d. of 18 mg/kg. In this form W. 3214 is only about twice as toxic as W.3065, whose intravenous m.l.d. is 30 mg/kg.

Given intraperitoneally to the mouse, the m.l.d. was 40 mg/kg, the substance being administered in a tragacanth suspension of the undissolved powder, as is done with feeding experiments. The powder suspension was usually absorbed within 24 hours, and at the latest 48 hours. Sections showed no irritation of the peritoneum which was smooth and shiny overall. Microscopically the organs of the abdomen were unchanged in form as well as constitution. There was a yellow coloration which was due to the absorbed product. In pharmacological experiments with the frog heart, W.3214, even in dilutions of 1:1,000,000, showed harm to the contractability and "reizbildung" which finally led to irreversible heart death.

Doses of 2 to 10 mg injected intravenously showed no acute action on the blood pressure of narcotized rabbits. 20 to 30 mg. led to a small prolonged drop. The simultaneous registered movements of the small intestines decreased, and there was a drop in tonus.

In contrast to the slight effect on the circulation, there occurs in warm blooded animals, especially under urethane narcosis, after 30 mg. W.3214 in rabbits an extraordinarily strong and prolonged tachypnea. This action was also established in rabbits under morphine

narcosis. However, it is not so pronounced and is shorter. In these experiments, one animal having 50 mg/animal (about 25 mg/kg of animal) died under respiratory failure.

In rabbits with fever, 50 mg. W.3214 per kg. of animal when fed as a suspension gave a small but lasting antipyretic action.

Much more caution must also be observed in applying tetrachlorsalicyl locally than is the case with dibrom-dioxybenzil. Particular caution is suggested if it is applied to strongly bleeding wounds or deep wounds. It is advised in such cases not to go higher than 0.1 gm.

W.-Elberfeld, 5.1.1945

H. Prof. Domagk, H. Dir. Dr. Schönhöfer

H. Dr. Mietzsch, H. Dr. Linsert

Prof. Weese.

(TRANSLATION OF REPORT FROM DR. HECHT TO PROF. HÖRLEIN,  
12 AUGUST 1944 - ORIGINAL REPORT OBTAINED FROM DR. HORLEIN  
23 APRIL 1945)

Toxicity of 5,5' -Dibrom-2,2'-dioxybenzil (W.3065)

This intensively yellow, water-insoluble compound is odorless and tasteless. Up to the present time, oral administration has not shown toxicity of any kind, when doses up to 1.0 gm/kg. were given to rats or 0.5 mg/kg. to cats.

In view of the expected mode of use, the action of the substance in contact with tissues was studied more closely and the application in the abdominal cavity was chosen because (1) local damage is earliest found in the sensitive tissues of the abdominal cavity and (2) the tissues of the abdominal cavity have optimal absorptional characteristics which would best measure the danger of absorptive toxicity by use of the substance in wound areas, etc.

Addendum 1 -- In these investigations we did not find local damage. In animals, which in the course of various periods had been killed by intraperitoneal administration, the substance lay in small lumps in various organs without producing hyperaemia, exudation, or adhesions.

Addendum 2 -- In rats, 1.0 gm/kg. (as a suspension in 0.9 percent NaCl) is tolerated when given intraperitoneally. Surprisingly, there was a relatively rapid absorption of the insoluble substance; after 48 hours apparently more than half had disappeared from the abdominal cavity and

after 4 days no traces were to be found. With 2.0 gm/kg. the absorption goes so rapidly that toxicity results. Of four animals so treated, three died in the first hour and the fourth after 17 hours, with uncharacteristic symptoms.

Rabbits were similarly treated intraperitoneally with various doses. A characteristic reaction was a rapidly appearing hyperpnea with cyanosis and relaxing action ("Schlaffheit") of the musculature, which lasts several hours and then the animals having 0.5 to 1.0 gm. doses recovered. The animals showed during the first few days strongly positive results for various albumin reactions in the urine. Closer study, however, led to the thought that this reaction apparently was due to an excretion of the substance in the urine, which gave a turbidity similar to the albumin reaction. However, this question has not yet been cleared up.

A cat received 0.5 g/kg. intraperitoneally; in contrast to the rabbit, the cat showed no toxic reactions, but did show similar urine reactions during the early days.

In contrast to the low toxicity when so administered is the smallness of the lethal doses by intravenous injection of the dissolved product. A solution in borax as well as in soda showed a fatal dose in the mouse of 30 mg/kg.

The above investigations led to the conclusion that the use of the product as powder on wounds or in wound cavities in doses as high as 1.0 gm. is unthinkable. No comment can yet be given regarding tolerance in clinical use.

#### PHARMAKOLOGISCHES LABORATORIUM

W.-Elberfeld, 12.8.44

Dr. Hecht

(TRANSLATION OF REPORT BY DR. LINSERT TO PROF. HÖRLEIN, DATED WUPPERTAL-ELBERFELD, 3 NOVEMBER 1944, and OBTAINED FROM PROF. HÖRLEIN 23 APRIL 1945)

#### Preparation of 5-5'-Dibromsalicil from 5-Bromsalicylaldehyde

5-5'-Dibromsalicil is obtained by the benzoin condensation from salicylaldehyde-methoxymethyl ether, oxidation of the benzoin so obtained by Fehling solution, and bromination of the salicil so obtained.

In place of salicylaldehyde, one may start with 5-bromsalicylaldehyde and obtain 5-5'-Dibromsalicil by the same means as in the case of salicylaldehyde. The yields for each of the intermediate steps are about equally good up to the dibromsalicylaldehyde itself (NOTE: Does he mean

bromsalicylaldehyde?); this derivative is obtained by the bromination of salicylaldehyde in a yield of about 60% of theory, while the conversion of salicyl into dibromsalicyl gives about 80% of theory, so that overall a slight decrease occurs in the total yield, calculated on salicylaldehyde.

#### 5-Bromsalicylaldehyde-Methoxymethylether

15 grams sodium powder is suspended in 100 cc. toluene and with stirring 30 cc. of absolute alcohol is dropped in. After conversion of the sodium into ethylate, there is slowly added 126 grams bromsalicylaldehyde in 400 cc. toluene and heated with stirring for about 2 hours at 100°. Then it is cooled to 10° and 50 grams of chloromethylether is added dropwise. After stirring for 12 hours, the product is diluted with ether, washed with dilute NaOH and water, dried over CaCl<sub>2</sub> and dried in vacuo.

5-bromsalicylaldehydemethoxymethylether is a light yellow liquid boiling at 145° at 5 mm. Yield, 50% of theory.

#### 5-5'-Dibrom-salicyl-methoxy-methylether.

A mixture of 114 grams of 5-brom-salicylaldehyde-methoxy-methyl ether, 120 cc. absolute alcohol, 12 grams KCN, and 120 cc. water is boiled for 2 hours under reflux. The alcoholic solution is diluted with water, extracted with ether, then the dark yellow ether residue is dissolved in a little alcohol and oxidized with 400 cc. of 16% copper sulfate solution + 600 cc. 20% alkaline Rochelle Salt solution. After cooling, the mixture of Cu O and dibrom-methoxymethyl-ether is filtered off and the dibrom derivative is purified by crystallization out of alcohol.

Yellowish platelets m.p. 116-117°. Yield - 58 grams = 50% of theory.

#### 5-5'-Dibromsalicyl

30 grams 5-5'-dibromsalicyl-methoxymethylether is dissolved in 150 cc. hot glacial acetic acid. To this hot solution are added 10 cc. of 15% sulfuric acid and 15 cc. water. After a short time the solution turns deep yellow, and 5-5'-dibromsalicyl separates as light yellow needles of m.p. 210°.

Yield 22.8 grams = 90% of theory.

## h. HORMONES

Hormones are manufactured principally at Elberfeld; Hoechst produces some also. The research and control work at Elberfeld is in charge of Prof. Hermann Weyland and Dr. Auhagen. Weyland was Professor in the University of Köln, and he is head of the department of Physiology and Biochemistry. He has 12 "akademische" assistants (Ph.D.), and 70 persons altogether in his research and biological control department. This group also takes care of vitamin research and control, under Dr. Auhagen.

The following hormones are manufactured at Elberfeld, in a fairly commodious plant having standard equipment for this kind of work:

- Prolan (gonadotropic)
- Unden (ovarian)
- Campolon (liver)
- Thrombin (not yet on market)
- Padutin (pancreas hormone)

Their laboratory collaborated with Kogl in work on Biotin, but gave it up when the U. S. publications appeared. Auhagen has been trying to find new antagonists for p-aminobenzoic acid, without success.

In the manufacture of Padutin, they dialize from cellophane bags, one in each of three tanks, for a period of 36 hours. Padutin is tested by measuring the heart amplitude in dogs.

Campolon is not tested for histamine content as a control measure. The only laboratory biological test used is a blood-pressure test. It is manufactured in a well-equipped building about 60 x 60 feet. Production in June 1943, regarded as a rather typical war month, was 108,000 2cc ampoules, 36,000 5cc, and 690,000 10cc.

Copies of the manufacturing processes were obtained.

## 1. VITAMINS

Vitamins. The products manufactured at Elberfeld include vitamins A (natural), B<sub>1</sub>, B<sub>2</sub>, D<sub>2</sub>, and D<sub>3</sub>. The research work is principally under the direction of Dr. Auhagen.

Vitamin A is the usual product derived from fish liver oils; they also prepare a concentrate. Vitamin D<sub>2</sub> is made from ergosterol in a room containing 10 irradiating units. A magnesium arc irradiates 25 grams of ergosterol in about 300 cc benzol in an annular quartz cell. Each unit is air cooled; if fire should break out, CO<sub>2</sub> is automatically injected. Vitamin D<sub>3</sub> has not yet been made in large volume.

Copies of the processes for manufacturing have been obtained.

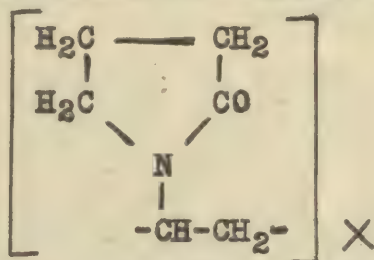
Interviewed: Drs. Weyland, Auhagen, Lutter, Rietz

## j. BLOOD SUBSTITUTES

### Periston.

The German government used military personnel as its source of human blood, part of which was dried in an army operated plant. Evidently they considered it impractical to use civilian blood donors on any appreciable scale, as such blood was found low in protein due to deficient diet. They also seem to have used smaller volumes of human blood per case than the Allies considered desirable. The Wehrmacht used more dried serum than dried plasma.

Periston was developed in the department of Dr. H. Weese, head of the pharmacology division. This is a 2½% colloidal solution of "Kollidon" (polyvinyl pyrrolidone), having the formula:



This colloid has a molecular weight of 6000 to 8000. We were informed that "Kollidon" is manufactured only at Ludwigshafen.

Periston is used mainly in shock. In the body it is broken down into amino acids. It remains in the circulation for 2 to 3 days. Even large doses (100 cc. per kilogram in the rabbit) cause no liver damage. The only effect is a transient albuminuria. No temperature rise occurred. No reactions have been reported in humans in a series of 200,000 to 300,000 injections which have been given. However, dogs do not tolerate the product, showing anaphylactic reactions. Dr. Weese stated it is not suitable in intoxication of infants.

To combat shock, 500 cc to 1000 cc is used. Blood (whole) is not mixed with nor given concurrently with Periston, but no explanation for this was given. Blood may be administered following the Periston. It was admitted that the product is inferior to blood in moribund cases.

Periston was first introduced for civilian use as a 3½% solution; the Wehrmacht used a 2½% solution.

Periston is described at some length in an article by

Weese in Medizinische Zeitschrift, No. 1, of which a photostat was obtained. It was manufactured at Leverkusen. The manufacturing formula is as follows:

NaCl cryst. D.A.B. 6	800 grams
KCl cryst. Analytical grade	42 grams
CaCl <sub>2</sub> . 6H <sub>2</sub> O cryst. analytical grade	50 grams
MgCl <sub>2</sub> . 6H <sub>2</sub> O analytical grade	0.5 grams
N/1 HCl	1710 cc = 1728.8 g.
NaHCO <sub>3</sub> D.A.B. 6	168 grams
Kollidon Solution, 20%	12,500 cc
Water, distilled	q.s. 100 liters = 101.3 kg.

NOTE: The Kollidon powder is dissolved in Elberfeld, filtered, and sterilized at 120°. The sterile solution is prepared to have a concentration of 20% (grams in kg) and must not vary from this.

The required amount of Kollidon solution is weighed into a 100-liter Jena flask and about 70 liters of warm distilled water (about 50°C.) is added. Then the accurately weighed salts are dissolved in the following order, with good stirring: NaCl, KCl, CaCl<sub>2</sub>, MgCl<sub>2</sub>. Then in a 10 liter flask the prescribed amount of NaHCO<sub>3</sub> is dissolved in about 6 to 7 liters of water and this is added gradually in a thin stream with careful stirring to the N/1 HCl in a flask. The solution foams due to evolution of CO<sub>2</sub>. When evolution stops, this solution is added to the Kollidon solution and the mixture is diluted to final volume with distilled water and stirred again.

The solution while still warm is filtered through a Seitz filter. It was found that a Seitz chamber filter with 6 to 8 filter plates of 30 cm. diameter was well adapted to this. Before the filtration, the entire filter system with the plates in place was carefully sterilized for 1/2 to 3/4 hour by streaming steam. The Periston solution is then drawn by vacuum into a 120 liter pressure vessel. The solution is then subjected to a rather low pressure, beginning at 0.3-0.5 "atu". Since the filter plates hold moisture from the steam sterilization, the first 3/4 to 1 liter is rejected. The next 5 liters is caught and re-added to the bulk so as to get rid of fibers. The clear solution is allowed to run into 10-liter storage flasks through a small fritted glass filter (G3). Filling of the filtered solution should take place the same day. 10 liters should filter in about 10 to 12 minutes; this usually requires some pressure increase, but

not over 1.5 "atu".

The solution is filled into 250 cc. and 500 cc. special ampoules. Great care must be taken to insure absolute cleanliness. The ampoules must be sterilized on the day following the manufacture of the solution. This is done in an autoclave for 1 hour at 105°C. in streaming steam.

The ampoules are stored for 3 weeks at 30 to 35°C. to permit any separation of material to be observed, then inspected.

Control:

100 cc = between 5-17 cc N/20 NaOH  
          between 28-95.2 cc. CO<sub>2</sub> per liter.  
          (1cc N/20 NaOH = 5.6 cc. CO<sub>2</sub> per liter.)

0.564 - 0.572 Cl

0.280 - 0.315 N

1.160 - 1.180 S-ash

pH = 6.0 - 7.0

Isotonicity = - 0.65° to - 0.70° C.

Toxicity - normal

Viscosity: 1.5 - 2.1

Sterile

## K. Insecticides and Insect Repellants.

### General Remarks:

The I.G. has been actively engaged in the commercial production of insecticides and in investigative work on new insecticides for a number of years. Before the war, efforts were directed primarily toward agents of agricultural importance. After the war began emphasis was placed on insecticides against arthropods of importance in military medicine, notably, lice. At least three research chemists were engaged in synthesizing new compounds for biological trials: Dr. Gerhardt Schrader of Leverkusen and later Elberfeld, worked on substitutes for nicotine; Dr. Werner Meiser of Elberfeld prepared variants on the DDT molecule; and Dr. Mintzmann of Leverkusen studied dye derivatives which had insecticidal properties. Tests to determine the effect of newly prepared compounds were made at Leverkusen by Dr. Bonrath; in a few instances, however, Prof. Kikuth at Elberfeld ran trials on anopheline mosquitoes. Lice, mosquitoes, flies, cornborers, moths, caterpillars and aphids were regularly used in biological tests; mites were never used and fleas rarely, if at all. The commercial manufacturing of insecticides was carried on entirely at Leverkusen.

Lauseto-(old). Lauseto - old is the trade name under which I.G. markets Gesarol. It contains DDT and a number of analogs of DDT and is subject to the Geigy patents. Lauseto is made with 1 mol. of chlorbenzol and 1 mol. of benzol combined with chloral in the presence of sulfuric acid. Lauseto-old is sold as a brown syrupy liquid containing 50% of active material which is dissolved in trichlorethylene. The commercial product also contains a wetting agent, Mersolatis, which makes up about 10% of the preparation. Mersolatis is made by chloresulfonation of hydrogenated paraffins of C<sub>12</sub> to C<sub>20</sub> chain length which are obtained by the Fischer Tropsch process. The insecticidal properties of Gesarol are well known and need not be discussed. Dr. Rüsck of Leverkusen stated that on the basis of their own work, they recommended that commercial Lauseto-old solution be used as an emulsion for the impregnation of clothes in the proportion of 25 cc. of Lauseto to 1 litre of water. The Wehrmacht used more dilute emulsions which Rüsck considered less satisfactory than his recommended strength. According to directions on cans of Lauseto-old supplied to the Wehrmacht, the following proportions were to be employed.

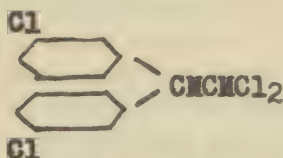
For impregnation of large amounts of clothes against lice a mixture of 3 litres of Lauseto and 300 litres of water was sufficient for 100 uniforms (shirts, drawers, socks and sweaters, about 6 pounds of clothes per uniform), and a mixture of 5 liters of Lauseto and 450 litres of water was adequate for 200 uniforms.

Garments were washed and rinsed and then impregnated by a final rinse in the lousicidal emulsion. Uniform coats were to receive additional treatment in the form of a spray of 1 - 2% Lauseto emulsion from a flit gun. For impregnation of a single uniform, 2 tablespoonsful of Lauseto were emulsified in  $1\frac{1}{2}$  litres of water, this mixture was to be used only once.

Clothes impregnated with Lauseto-old emulsion, 25 cc./litre, remain lousicidal for 3 months if not washed. One or two washes in lukewarm water reduce the protective action only slightly. Washing in boiling hot water or dry cleaning takes out all the active material, furthermore, pressing with a hot iron destroys an appreciable amount of the lousicidal agent.

Informants: Drs. Bayer, Redies, Räscher, and Stottard.

Me 1700. Prepared by Dr. Meiser on an experimental scale, not commercial. Formula is

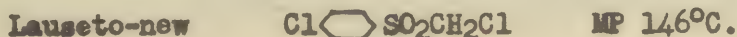


and varies from Gesarol in having 2 instead of 3 chlorine atoms in chain. Physical and insecticidal properties similar to Gesarol; as effective against lice and almost as effective against bed bugs and mosquitoes, caterpillars, moths, flies and cornborers. Cannot be produced without some of trichlor. compound, therefore subject to Geigy patent.

No other substitution compounds approach effectiveness of Gesarol or Me 1700. Nitro, acetyl, sulfonamide etc., substitution of the chlorine on the rings, substitution of other halogen on other end of molecule and lengthening the chain all results in less active compounds.

Interview - Dr. Meiser.

Lauseto-new. This compound unrelated to Gesarol and therefore not subject to the Geigy patents was prepared in the Dye Department, Leverkusen. It is made by reacting chlorobenzene with chlorosulfonic acid and reducing with zinc dust to  $\text{ClSO}_2\text{Na}$  which is in turn reacted with sodium dichloroacetate, then it is acidified and  $\text{CO}_2$  driven off to give



Lauseto-new is supplied for use in two forms: (1) a fairly stable heavy suspension containing about 50% active material plus bentonite and the emulsifying agent which is used in Lauseto-old, and (2) large tablets weighing 25 gm which contain 44% active substance plus bentonite, talcum and chalk.

Lauseto-new is not toxic to human beings. It is said to be five times more active against lice than is Gesarol, i.e., one fifth the concentration has the same lousicidal effect. The product is also active against bed bugs, but is of little value against flies or aphids. It has not been tested against mosquitoes, flies or mites.

The product has not been marketed, but since dye stuff equipment alone is used in its manufacture, it could be produced in amounts up to 50 tons/month.

The Leverkusen workers recommend that 10 cc. of Lauseto-new suspension be diluted in 1 litre of water for a rinse for the impregnation of clothes against lice. With occasional stirring this dilute suspension can be used for the impregnation of a number of lots of clothes; the exact poundage of clothes that a given amount of this suspension will render lousicidal has not been determined. It will be noted that although Lauseto-new is supposed to be 5 times as active as Lauseto-old, the Leverkusen group employs the new substance at a concentration of only 1/2.5 that of the old.

The Lauseto-new tablets are intended for issue to an individual soldier for impregnation of his own clothes. The tablet is pounded to powder and a suspension prepared by the gradual addition of 5 litres of water. The resultant suspension is relatively unstable and must be stirred frequently. It is intended for only one batch of clothes and is then discarded.

Cloth impregnated with Lauseto-new remains lousicidal about as long as that treated with Gesarol. Lauseto-new like the old, is removed from cloth by washing in hot water, but it is less affected by heat, so that ironing does not reduce greatly the activity of treated fabric.

Informants: Drs. Redies, Bayer, Rüsch, Wenk, Bonrath, and Stotter.

D1210.

This is a mixture of equal parts of  $\text{SO}_2\text{CH}_2\text{Cl}$  &  $\text{Cl}-\text{SO}_2\text{CH}_2\text{OH}$  which belong in the same general group as lauseto new. It has been tested experimentally but not manufactured commercially. This is the best preparation yet obtained against bed bugs. It has some effect against lice, but is not effective against flies or mosquitoes.

Interviewed - Drs. Rüsch, Wenk, Bonrath and Stotter.

Samples obtained - D1210 - solution.  
D1210 - powder.

Lucex. Lucex is less effective against lice than Lauseto-new but is cheaper to manufacture. This substance is produced by ethylating chlorobenzene and then chlorinating the side chain in the presence of light to obtain a mixture having 3 or 4 chlorine atoms in the side chain. It is dispensed as a powder containing 6% active material and the remainder inert filler consisting of a mixture of 1/3 and 2/3 talc. About 40 tons of the powder have been manufactured at Leverkusen. Lucex was used principally on foreign workers for the control of lousiness. It is somewhat irritating to the skin. (Informants: Drs. Redies and Bayer).

Production capacities of I.G. Plants for Lousicidal Agents.

<u>I. G. Plant</u>	<u>Product</u>	<u>Capacity in tons/</u> <u>month.</u>
Leverkusen	(1) Lauseto - old (Gesarol)	100
	(2) Lauseto - new	50
Wolfen (Near Bitterfeld)	(1) Lauseto - old	120
Höchst	(1) Fluorogesarol (GIX)*	70

\*GIX is produced by the combination of 2 mols of fluorobenzene with one of chloral in the presence of sulphuric acid. It is said to be more effective than Gesarol against flies and mosquitoes but less effective against lice. Equipment used for manufacture of GIX could be readily adapted for Gesarol.

Information on Leverkusen and Wolfen obtained from Dr. Wenk, who does not know whether the latter plant has suffered recent damage. Information on Höchst obtained from Dr. Bockmühl of Höchst.

Bladan. This hexaethyl ester of tetraphosphoric acid,  $((C_2H_5O)_2PO)_3$  PO is marketed as an agricultural insecticide for the control of aphids (plant lice). It is prepared by reacting 1 mol of phosphorus oxychloride with 3 mols of triethylenephosphate in the presence of a slight excess of the latter. It is supplied as a mixture containing 60-70% of active material with the balance consisting of equal parts of a solvent (xylol) and a wetting agent.

Bladan has a nicotine-like effect on aphids and is said to be more active than nicotine. In dilute solution such as that used as a plant spray Bladan decomposes at a moderately rapid rate.

Informants - Drs. Klebert, Bayer, Rüsck, Wenk, Bonrath and Stotter.

## Mosquito Repellents.

A new preparation designated 50/181 with the formula  $\text{CCl}_3\text{CO}\text{NHC}_2\text{H}_5$  has been found to be highly active as a mosquito repellent. The substance trichloroacetylchloroethylamide, was synthesized by Dr. Schweitzer of Leverkusen who was not available and whose laboratory notes could not be found. The preparation of 50/181 according to Dr. Bayer is as follows:

Trichloroacetic acid methyl ester is treated at an elevated temperature with an aqueous solution of chloroethylamine; after a short period of boiling the chloroethylamide separates in practically pure form. Chloroethylamine used in the above reaction is obtained by treating ethenolamine with thionyl chloride in accordance with the published literature. About 4 pounds of the active material have been prepared; this was done for the first time in February 1945. The repellent solution is made according to the following prescription: 7.5% trichloroacetylchloroethylamide, 1.25%  $\text{Ca Cl}_2$ , 1.25%  $\text{Mg Cl}_2$ , 60%  $\text{C}_2\text{H}_5\text{OH}$  absolute, and 30%  $\text{H}_2\text{O}$  dist.

50/181 has been tested against one strain of culicine mosquitoes, but not against anophelines or other biting insects. No skin irritations have developed on the few persons on whom the repellents solution has been used. Skin, clothes and sox treated with the solution have a repellent effect for a period of of about 6 hours.

The only other substance, among the many examined at Leverkusen which was found to have a repellent effect against mosquitoes was diethylphthalate. Preparation 50/181 is definitely superior to this phthalate compound. No information was forthcoming when a general question was asked regarding the effectiveness of other esters of phthalic acid.

Informants: Drs. Bayer, Rüsch, Bonrath, and Stotter.

## 1. Miscellaneous

The barbiturates manufactured at Elberfeld include Veronal, Luminal, Phanodorm, Prominal, and Evipan. Their research department did a great deal of work in this field; in the period around 1928 they studied 300 to 400 compounds to find a successor to Luminal. They also made a series of hydantoins, including diphenyl hydantoin, none of which is regarded by them to be as satisfactory as Luminal in epilepsy.

Evipan is sold not only as the sodium salt for injection, but also as the free acid for oral use, in the form of 0.5 gram tablets to give prompt sleep lasting 3 to 5 hours. Only a few cases of reaction (edema) have been reported. In 1940 or 1941, Henniker at Elberfeld made the surprising observation that the salt of tetraethylammonium hydroxide with Prominal is of low toxicity orally, but quite toxic if injected. Since their original "Prominal-Na Tropfen" tends to precipitate, they expect to substitute the above product in the form of a viscous flavored solution so that it will not be injected.

Prof. Schönhofen, who readily supplied information, stated that Luminal, Phanodorm, Prominal, and Evipan are very widely used. Their normal production of each Luminal and Phanodorm was stated by Dr. Schellenberg, of Leverkusen, to be 2 metric tons per month.

For the manufacture of barbituric acid derivatives they use the cyanoacetic ester method; dicyandiamide is converted to cyanoacetic acid and this to the ester, in a 2,000 liter kettle. Veronal and Phanodorm are crystallized out of water, Luminal out of alcohol. A few years ago they partially equipped a new barbiturate building containing three 8,000 liter kettles, and this is in partial production.

Kikuth stated that their attempts at chemotherapy of influenza had been entirely fruitless. He does not seem to have a very high opinion of Bayer-205 (Germanin, Naganol), but considers it to be as good as any product with which he is acquainted.

The I.G. sales department in July 1944, ordered 2,600 kg atabrine for the army, plus 500 kg for civilian sale, plus 15 million tablets. All together, they actually wanted 12,000 kg atabrine per month, but the manufacturing department, due to bombing results, and lack of materials and manpower, could not meet the schedule.

Of Campolon (liver extract), manufacture in June 1943, (regarded as a typical month) was 108,000 2-cc, 36,000 5-cc, and 690,000 10-cc ampoules. Other production figures:

Evipan, -16,000 0.5 gram and 198,000 1.0 gram ampoules (June 1943); tablets 0.5 gram, 2 million (July 1944)

Chinoplasmin - 3 million tablets per month in 1942 - sales later dropped off.

Cignolin - 60 kg per month (June 1943)

Pasmochin - 3 million of 0.01 g/mo/ in 1942  
2 million of 0.02 g/mo. in 1942

Dolantin tablets - 400,000; solution, 800 liters (July, 1944)

Ergosterol - 25 kg/mo.

Vigsntol in oil - 25,000 10cc/mo.

Zephirol Solution - 10,000 liters per mo.  
This product was partly used for impregnating paper strips for the sterilization of the hands.

Panflavin Pastillen - normal 15 million/mo.

Mitigal, 25 tons/mo

Istizin - 3 tons/mo. human, 3 tons for veterinary use.

Impletol - 25,000/mo.

Nicotinic Acid is not manufactured by I.G. Elberfeld, but was purchased at 35 marks per kg from a firm in Hamburg, which was believed to be using the process of oxidation of nicotine by potassium permanganate.

Yatren was stated to be a very large item, but sales figures were not obtained.

It was pointed out that sales during the war years generally exceeded the normal demand, but production difficulties caused 1944 output in many cases to be considerably below normal.

### Aspirin

Production 25 tons/mo.

Elberfeld is claimed to have the only aspirin plant of the I.G.

## Process

There are 4 acetylators and raw materials per batch are  
380 kg salicylic acid  
425 kg 50% benzol 50% ligroin  
365 kg acetic anhydride.

NOTE: Ligroin is a "paraffin" solvent boiling at 80-105°C.

The ingredients are first mixed and run thru a filter to the acetylator which is a silver plated kettle with a stainless steel top equipped with water bath and reflux condenser where they are heated for 3.5 - 4 hrs., to a minimum temperature of 75°C and kept at this temperature for 2.5 hrs. The water bath is then drained, the whole stirred for 4.5 hrs. at 60°C, then water cooling begun at a rate of 3°C drop per hour at 20°C. Inside the water bath are brine coils by which temperature is brought to 6°C in 4 hours.

The batch is removed thru a valve in the bottom to a suction filter of aluminum with a stirrer which is filled with CO<sub>2</sub> to avoid fires from static electric charges. Three washes are given of 1/2 hr. each with the benzol-ligroin, 340 kg solvent for each wash.

The crystals are brought to the drier in a truck where they are placed on trays in wagons in the drier. When full, the drier is heated to 60-70°C after 30 hrs. the chamber is emptied and the product sized and packed. The gases from the drier pass thru an activated charcoal recovery system to recover the benzol-ligroin.

The mother liquor from the process is collected and from 2500 l. in a kettle 2000 kg are distilled off up to 88°, the distillate being acetic acid, and benzol-ligroin. The residue goes thru an aluminum filter to a 600 l. silver kettle in which after cooling aspirin settles out and is filtered, dried and returned to the beginning of the next batch. The distillate is washed in a tower of stainless steel in which it rises against descending water to remove acetic acid which is recovered at 50% strength.

## Salol

Production 4 tons/mo.

### Bill of materials

142 kg phenol  
190 kg toluol (for washing)  
210 kg salicylic acid  
21 kg phosphorus trichloride  
71.7 kg phosphorus oxychloride

Phenol, salicylic and the phosphorus tri and oxychlorides are heated together, phosphoric acid separates and the salol is washed and crystallized.

Yield is 116% of weight of salicylic used.

Interviewed: Drs. Lutter, Rietz, Mr. Sinkel.

m. INDEX OF DOCUMENTS OBTAINED AT I. G. PLANT,  
ELBERFELD.

Folder No. 1

Loose papers

1. Thioglycolic Acid, Preparation, reprint from Angewandte Chemie 46, 780, (1933), by Franz Schütz, Cologne-Marienburg.
2. Methyldebenal (Sulfamerazine), work instructions by Dr. Medick (5/25/44).
3. Sulfaguanidine, work instructions by Dr. Medick (5/25/44)
4. Index of work instructions with intermediates.
5. Vitamin A, Memo, handwritten to Dr. Sutter from Dr. Moré (10/21/32).
6. List of yields from various products (10/4/37).
7. Acricyl, work instructions by Dr. Wolff (11/27/36).
8. Ascaridol, work instructions by Dr. Moré (9/29/33).
9. Dentalol (Damol solution, 5% and 10%) (5/18/37).
10. Diethanolamine, work instructions by Dr. Moré (11/2/33).
11. Novel alcohol, work instructions (7/8/39).
12. Novolketone, work instructions (11/20/37).
13. Novolketone from acetopropylalcohol, preparation by Dr. Andersag (12/6/39).
14. Novolid salts, work instructions (11/20/37).
15. Novolid, work instructions by Dr. Moré (8/3/29).
16. Novol ester, crude, work preparation by Dr. Moré (8/3/29).
17. Novoldiamine (addition to work instructions) (12/4/42).
18. Carbon copy of 17.
19. Novoldiamine, preparation (10/6/41).
20. Carbon copy of 19.
21. Novoldiamine, preparation (5/15/37).
22. Novoldiamine, preparation, by Dr. Schröter (12/11/34).
23. Pelviric acid (3.5 diiodo-4-piperidone-1 acetic acid), work preparation by Dr. Zimmerman (12/29/42).
24. Pelviric acid, additions and modifications for the preparation (2/15/35).
25. Septazin, work preparation by Dr. Zimmerman (1/27/41).
26. Sipon (basic bismuth salt of diiodoadipic acid), preparation by Dr. Zimmerman (1/16/34).
27. Voganölen (Vitamin A preparation), memo from Dr. V. Dobeneck dated 7/24/34 correcting part of his report of 8/29/34.

Bound alphabetized present manufacturing directions by  
Dr. Zimmerman

28. Index for the following methods.

29. Mejolan (5/19/42).
30. Abrodil (2/20/43).
31. Same
32. Perabrodil-ethanol (5/19/42).
33. Ascaridol (5/19/42).
34. Diethanolamine (5/19/42).
35. Immetal (diiodoerucic acid, isobutyl ester) (5/19/42).
36. Behenol saure (5/19/42).
37. Ribose by reduction of Ribolactone (9/13/43).
38. Lactoflavin (Vitamin B<sub>2</sub>) from Ribonitramine (9/27/43).
39. Novol alcohol (5/15/37 and 5/19/42).
40. Novol alcohol (5/20/42).
41. Novoldiamine (12/11/34).
42. Novoldiamine (11/3/33).
43. Novolketone (5/19/42).
44. Novolketone from Acetopropyl alcohol (12/6/39).
45. Novolid sat (5/19/42).
46. Novolid (8/3/29).
47. Novol ester, crude (8/3/29).
48. Novoldiamine, additions (12/4/42).
49. Novoldiamine (10/6/41) and (5/19/42).
50. Novoldiamine (5/15/37).
51. Pelviric acid and its intermediates (8/1/33).
52. Pelviric acid and its intermediates, additions and improvements (2/15/35) and (5/19/42).
53. Pelviric acid (12/29/42).
54. Sarin (sarcosin anhydride) (5/11/37) and (5/19/42).
55. Sipon (1/16/34) and (5/19/42).
56. Thioglycolic acid (1/4/34) and 5/19/42).
57. Thioglycolic acid (12/29/31).
58. Vogan (11/17/37).
59. Vogan (12/30/37).
60. Vogan (12/30/37).
61. Vogan (11/17/39) and (5/20/42).
62. Vogan (5/20/37).

## Folder No. 2

### Bound manufacturing methods for A. T. Cellulose - Dr. Leuchs.

1. Amylokoll (D), (4/30/42).
2. A. T. Cellulose B. )  
A. T. Cellulose B. S)- (11/13/36)  
Benzyl cellulose )
3. Cellappret "feucht" (2/11/41).

## Folder No. 3 (In French - all from "Rhône-Poulenc")

### Unbound

1. Antergau ampoules, method of preparation (10/13/43).

2. Antergau ampoules, packaging (10/13/43).
3. Antergau ampoules, method of analysis (10/13/43).  
Bound papers
4. Index to papers.
5. Letter from Grillet to Hörlein re Antergau (10/15/43).
6. Antergau, method of preparation (10/13/43).
7. Antergau methane sulfonate, method of preparation (10/14/43).
8. Antergau, observations on preparation (10/15/43).
9. Antergau, method of analysis (10/13/43).
10. Antergau methanesulfonate, method of analysis (10/13/43).
11. Antergau ampoules 0.10 g., method of manufacture (10/13/43).
12. Antergau ampoules 0.05 g. for children, method of manufacture (10/13/43).
13. Antergau ampoules, packaging 0.1 g. (10/13/43).
14. Antergau ampoules, packaging 0.05 g. (10/13/43).
15. Antergau ampoules, method of analysis (10/13/43).
16. Blueprint of plant operations (10/13/43).
17. Letter from Rhone-Poulenc to Hörlein re preparation of Antergau ampoules (8/13/43).
18. Antergau ampoules, methods (8/13/43).

#### Folder No. 4

1. Blueprint of Evaporator for hexamine plant, I.G.Elberfeld (unbound).  
Bound papers (Manufacturing methods by Dr. Hoffmann).
2. Index
3. Aldol - a - naphthylamine powder (7/1/44).
4. Aldol - a - naphthylamine powder (11/1/41).
5. Aldol - a - naphthylamine resin (7/1/44).
6. Aldol - a - Naphthylamine - B (7/1/44).
7. Aldol - a - Naphthylamine - resin (11/1/41).
8. Aldol - a - naphthylamine - B (11/1/41).
9. Beschleuniger 576 (accelerator 576), (7/1/44).
10. Beschleuniger 576 (accelerator 576), (11/1/41).
11. Beschleuniger 576 extra, (7/1/44).
12. Beschleuniger 576 extra, (11/1/41).
13. Plastol L B (11/21/41).
14. T.C. Resin (7/1/44).
15. T.C. Resin (11/1/41).
16. T.C. Resin (5/12/44).
17. T.C. Harz (8/16/34).
18. Vulkazit F.P. (7/1/44).
19. Vulkazot F.P. (11/1/41).

#### Folder No. 5

Bound papers (Manufacturing processes by Dr. Dörr)

1. Amylene hydrate, works preparation (2/1/44).
2. Blueprint of apparatus (4/21/44).
3. Amylene hydrate, works preparation (4/1/44).
4. Antisol, works preparation (2/8/43).
5. Gravitol, works preparation (2/8/43).
6. Gravitol 1,5 salt (salt of naphthalene - 1,5 desulfonic acid), works preparation (2/11/43).
7. Iocapral, works preparation (3/1/43).
8. Methylacetamide, works preparation (2/8/43).
9. Pardinon, outline of synthesis (by Dr. Medick) (3/10/43).
10. Pardinon, amounts of materials used in production and manufacturing method (by Dr. Medick) (3/10/43).

Folder No. 6

Bound papers (Manufacturing methods by Dr. Jaeger)

1. Index.
2. Alasin (acetylaladin), (8/26/42).
3. Adalin (12/12/30).
4. Afridol (3/10/40).
5. Allyl-lonester (3/17/43).
6. Allylphenylbarbituric acid (4/1/43).
7. Anonethylester M, (5/11/42).
8. Anonester M (5/8/42).
9. Aristochin (5/12/43).
10. C - ester (4/28/42).
11. Quinine base (5/19/43).
12. Compral (8/26/42).
13. Dicyanid (5/19/43).
14. Diester M (4/20/42).
15. Endormester (11/19/41).
16. Evipan (10/17/41).
17. Evipan sodium (11/13/41).
18. Hydrastinin (Hce) (8/18/42).
19. Homopiperonylamine by reduction of homopiperonal-oxine at lead cathode (9/2/38).
20. Luminal (10/15/41).
21. Luminal Sodium (4/1/43).
22. Novasurol (9/7/42).
23. Novasurol solution (9/7/42).
24. ON - sodium (8/22/42).
25. Phanidorn (12/31/32).
26. Prominal (4/21/42).
27. Prominal solution T (salt which tebraethyl ammonia hydroxide) (3/17/43).
28. Phanidorn (Calcium) (4/1/43).
29. Benzoic acid mono glycolestr (9/8/42).
30. Spirossal (9/7/42).

31. Veronal A (5/6/43).
32. Veronal B (12/4/40).
33. Veronal B - appendix (10/2/41).
34. Veronal sodium (4/43).
35. Wegonsalz (8/22/42).

Folder No. 7

Bound papers (Manufacturing methods by Dr. Lautenschla-

1. Index ger.)
2. Amichin (3/13/45).
3. Amichin, reduction apparatus, blueprint (3/13/45).
4. Aricyl (11/28/38).
5. Benzyl Antileprol (2/7/34).
6. Campoferron (2/23/43).
7. Campolon (4/30/43).
8. Campolon (7/23/36).
9. Candiolin (11/6/36).
10. Casein (10/8/36).
11. Cholesterinacetate (2/2/40).
12. Damol Solution (Dontalol), (12/31/42).
13. Eldoform (1/22/40).
14. Galactose (3/20/45).
15. Galactose, observations on preparation (3/20/45).
16. Galactose (11/7/41).
17. Heptin (5/8/31).
18. 1-Heptin from 1- and 2- heptin (12/8/26).
19. Hexeton (1/15/24).
20. Histamine (1/30/40).
21. Histidin (8/1/24).
22. Igeton - concentrate (Dr. Wolff) (8/31/33).
23. Invertase (Dr. Wolff) (2/7/40).
24. Iodisan (Dr. Wolff) (6/24/36).
25. Methyl iodide (Dr. Contelle) (9/22/33).
26. Iothion (Dr. Wolff) (5/26/39).
27. Kollidon, pure (2/23/43) crude Kollidon is made at Ludwigshafen.
28. Kollidon solution (20% for Periston)(2/22/43).
29. Mykol (Dr. Wolff) (6/5/36).
30. Manetol K.S. (3/5/43).
31. Murnil (Dr. Wolff) (11/1/37).
32. Padutin (3/5/43) from urine.
33. Padutin (3/4/43) from pancreas.
34. Para-oxy, (p-hydroxyphenylethylamine, hydrochloride) (Dr. Wolff) (4/21/42).
35. Prolon (Dr. Wolff) (7/27/36).
36. Beef brain for Lipatren (3/3/43).
37. Beef brain, dried for Lipatren Tablets.

38. Sajodin (1/5/43).
39. Solarsonic acid (Dr. Wolff) (4/29/36).
40. Carbon tetrachloride, purification (Dr. M. Kuhn) (1/5/43)
41. Tibatin (3/23/45).
42. Tibatin (11/7/41).
43. Tyrosin (Dr. Wolff) (8/1/24).
44. Unden from Mare urine (2/26/44).
45. Oestron - benzoylestoin (4/13/43).
46. Undenbenzoate (3/3/43).
47. Veduril for ampoules (12/30/41).
48. Vaduril for tablets (12/30/41).
49. Yatric acid (3/28/45).
50. Yatric acid - outline of synthesis (Dr. Contelle)  
(5/27/32).

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1. Index
2. Antimonoxyd paste (Dr. Bauer) (1/23/41).
3. Copy of 2.
4. Antimosan (Dr. Schmidt) (2/28/44).
5. Antimosan, solid (ppt. with methanol) (Dr. Schmidt)  
(2/28/44).
6. Antimosan (Fuadin powder) (Dr. Bauer) (11/11/41).
7. Astrosol (Dr. Bauer) (7/12/40).
8. Benzylphenol (Musch - Bephol), from Dibenzylether  
(Dr. Gundlach) (7/19/35).
9. Bephols - mixed, separation (Dr. Gundlach) (10/8/41).
10. Brenznatrium (pyrocatechol - bisodium sulfonate) (8/20/44)
11. Brenznatrium, apparatus (9/15/44).
12. Brenznatrium, memo re: excess nace (4/7/43).
13. Brenznatrium (Dr. Bauer) (5/9/40).
14. Bromocoll (Dr. Gundlach) (10/21/41).
15. Butolan (Dr. Bauer) (12/20/40).
16. Castrix - K rner (new description) (Dr. Gundlach)  
(11/4/44).
17. Castrix - K rner (9/26/44).
18. Castrix - K rner (Dr. Gundlach) (1/20/44).
19. Castrix - K rner (Dr. Rietz) (3/30/43).
20. Castrix - K rner (Dr. Gundlach) (6/16/43).
21. Coryfin (Dr. Bauer) (12/12/40).
22. Eleudron (Sulfathioyl) (Dr. Bauer) (12/11/41).
23. Eleudron - intermediate needed for 1000 Kg.
24. Eumydrin (Dr. Gundlach) (10/2/41).
25. Filtragol (Dr. Gundlach) (11/5/41).
26. Feed extraction (to make vitamin free feed) (Dr. Wolff)  
(11/21/36).

Folder No. 9

- Bound papers (Manufacturing methods)(Dr. Grundlach unless otherwise noted).
1. Isitizin (Dr. Bauer) (10/14/41).
  2. Tin sponge (Dr. Gunzler) (3/23/32).
  3. Marfanil (3/24/44).
  4. Marfanil, intermediate and residues for one new (3/25/44)
  5. Same as 4.
  6. Marfanil apparatus (3/21/44).
  7. Marfanil blueprint of process (6/22/43), 4 sheets.
  8. Marfanil, explanation of blueprints (6/23/43).
  9. Same as 8.
  10. Same as 9.
  11. Marfanil, requirements for 1000 Kg. (9/19/42).
  12. Mesudin (Marfanil) (11/5/41).
  13. Mitigal, apparatus for distillation (9/21/44).
  14. Mitigal, apparatus for U.S.A. (10/3/38).
  15. Mitigal, blueprint (10/4/38).
  16. Mitigal (10/15/38).
  17. Mitigal, blueprint (8/20/37).
  18. Mitigal
  19. Mitigal, method for U.S.A. (10/3/38).
  20. Mitigal, distillation (9/22/38).
  21. Mitigal, (10/4/38).
  22. Mitigal (12/21/43).
  23. Michin A, (11/4/44).
  24. Michin (Dr. Bauer) (1/22/42).
  25. Michin, solution (9/22/44).
  26. Novolbromide (11/7/41).
  27. Novantisolsäure (3/7/44).
  28. Same as 27.
  29. Novantisolsäure (10/25/43).
  30. Novantisolsäure (Dr. Bauer) (10/26/40).
  31. Oxychine crude, working up (2/16/44).
  32. Oxychine solution (10/12/44).
  33. Oxychine (10/18/41).
  34. Oxychinsäure (10/11/41).
  35. Oxychinsulfosäure (10/9/41), also Oxychinsäure.
  36. Paraform - mixture ); Ammonia - liberator ) (10/7/41).
  37. Diphen (Dr. Bauer) (11/8/40).
  38. Piperazin (Dr. Bauer) (11/8/40).
  39. Presinol concentrate (Dr. Dörr) (6/19/40).
  40. Presinol solution (Dr. Dörr) (6/19/40).
  41. Prontyl compounds - requirements for 1000 Kg. (12/19/41).
  42. Astrocid (sulfanilamide) (Dr. Bauer) (10/7/41).
  43. Prontosilbase, requirements for 1000 Kg. (12/19/41).
  44. Prontosilbase ) pure (6/10/41)  
Prontosil rubrum )

45. Prontosil base (Dr. Bauer) (6/30/41).
46. Prontosil S (6/10/44).
47. Prontosil S (Dr. Bauer) (9/23/41).
48. Prontargol (10/31/41).
49. Pyrazin (2.5 Dimethylpyrazin) (9/24/42).

#### Folder No. 10

##### Bound papers (Manufacturing processes)

1. Salol (Dr. Bauer) (10/18/40).
2. Salophen (Dr. Grundlach) (1/30/40).
3. Salphenbase (Dr. Grundlach) (1/30/40).
4. Salophen - crude (acetylation of salophenbase) (Dr. Grundlach) (1/30/40).
5. Salphen - pure (Dr. Grundlach) (1/30/40).
6. Soap and soap solutions (Dr. Grundlach) (10/28/41).
7. Solustibosan (Dr. Schmidt) (11/2/42).
8. Somatose (Dr. Grundlach) (11/28/41).
9. Somatose (Dr. Contelle) (7/25/29).
10. Sulfapyridine - list of materials for 100 Kg.
11. Sulfapyridine - (Dr. Grundlach) (9/27/43).
12. Sulfapyridine (Dr. Bauer) (7/1/40).
13. Sulfapyridine - sodium (Dr. Dörr) (12/4/40).
14. Sulfosolkalk (calcium cresolsulfonate) (Dr. Grundlach), (4/26/40).
15. Kolkalk (calcium quatsolsulfonate) (Dr. Grundlach), (4/26/40).
16. Tutocaine residues, recovery (Dr. Grundlach) (4/45).
17. Tannigen, old method (Dr. Grundlach) (10/7/41).
18. Tutocaine (Dr. Grundlach) (1/3/42).
19. Diparamide (Dr. Bauer) 2/14/41).
20. Ulrion A (3/15/40).
21. Monoparamide (Dr. Bauer) (10/30/40).
22. Ulrion B (Dr. Dörr) (4/8/40).
23. Ulrion C (Dr. Dörr) (3/29/40).
24. Voluntal (Trichlorethylurethan) (Dr. Grundlach) (11/23/40).
25. Vulkanol B (mixed product from benzyl naphthalenes) (Dr. Grundlach) (3/12/40).
26. Wagon - oil (Dr. Grundlach)
27. Zelio - Körner (Dr. Grundlach) (6/16/43).

#### Folder No. 11

##### Bound papers (Manufacturing methods)

1. Index.
2. Acetsäure (Dr. Wiegand) (9/28/42).
3. Acetsäure - blueprint of apparatus (9/29/42).
4. Acetsäure (Dr. Wiegand) (11/22/41).

5. Acetyl Benzylamine (Dr. Wiegand) (8/27/42).
6. Acetylsalicylic acid - L, Höchst method (2/6/29).
7. Acetylsalicylic acid - S, Höchst method (2/6/29).
8. Acidol (1/30/40).
9. Aspirin, mercury content, memo (7/31/44).
10. Aspirin (12/6/30).
11. Acetu acid. )  
Benzol-Sigroni mixtures } recovery (7/25/35).
12. 4,4' diamino diphenyl sulfone (Dr. Wiegand) (5/4/42).
13. Germanin - Naganol (Dr. Wiegand) (11/18/41).
14. Germanin - Naganol (Dr. Wiegand) (11/20/41) 44 sheets.
15. Helmitol (2/1/40).
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17. Heroin hydrochloride
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19. Heroin mother liquors and residues, recovery (3/9/38).
20. Hexa - pure (Dr. Wiegand) (8/1/42).
21. Hexa, quarterly report of Dr. Wassmuth (3/25/41).
22. Methylenesäure (Dr. Wassmuth) (2/1/40).
23. Strychnine methylarsenic acid salt (3/1/23).
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27. Monoacetylurea - Dr. Wiegand (5/4/42).
28. Ortizon from tech. urea (1/12/30).
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2. Aethsäure (5/20/42).
3. Athylonester M (ethylphenylmalonic acid dimethyl ester) (5/22/42).
4. Athylonsäure (ethylphenylmalonic acid) (12/21/44).
5. Allyl alcohol )  
Allyl bromide } (5/26/42).
6. Amichin (Dr. Gänzler) (2/3/42).
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8. A. T. 10 resin (4/10/43).
9. A. T. 10 resin, apparatus blueprint (4/2/43).
10. A. T. 10 stock solution (4/10/43).
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12. Benzylcyanide (Dr. Gänzler) (11/9/42).
13. Succinic acid ester (Dr. Gänzler) (5/10/42).
14. Ethylbromide, test )  
Ethylbromide, dist ) (Dr. Gänzler) (11/10/36).

15. Bromal (Dr. Gänzler) (10/29/41).
16. Hydrogen bromide (Dr. Müller) (6/13/34).
17. Ceresan - nassbeize (Dr. Gänzler) (4/1/43).
18. Ceresan - nassbeize (especially made for Denmark)(Dr. Gänzler).
19. C - ester (Dr. Gänzler) (6/2/42).
20. Cignolin (Dr. Gänzler) (5/10/35).
21. Cyanacetamide (Dr. Gänzler) (5/18/42).
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23. Cyren, additions (Dr. Medick)(7/19/40).
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25. Denteryl (Dr. Gänzler) (3/19/43).
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27. Dibenzoate, dibenzoate of 7-hydroxycholesterol (Dr. Gänzler)
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33. Isopropyl alcohol from Avertin and Trichloreitiano1 (Dr. Gänzler) (6/21/32).
34. Keto (7 keto-cholesterol acetate) (Dr. Gänzler) (10/13/39).
35. Vitamin D<sub>2</sub>, crystalline (Dr. Linsert) (12/16/36).
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37. Lunchloride, crude wet (methoxyethyl mercuric chloride) (Dr. Gänzler) (6/17/41).
38. Lunchloride, tablet mass (Dr. Gänzler)(6/17/41).
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57. Thiuran (Dr. Gänzler) (11/10/42).
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68. Vigantol, strong (Dr. Gänzler) (12/18/42).
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73. Vulkacit 1000 (Dr. Gänzler) (6/10/36).
74. W - 491 (2-chlor-4-dimethylamino-6 methyl-pyrimidin), (Dr. Gänzler).
75. Urazil (Dr. Gunzler) (10/27/44).
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77. Zepherol concentrate (Dr. Gänzler) (9/10/37).
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79. Zepherol intermediate solution (Dr. Gänzler) (8-25-42)

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1. Verfahren zur Herstellung von Binitrochlorbenzol soh (Dr. Baltes).
2. Verfahren zur Herstellung von Binitrochlorbenzol P. (Dr. Baltes).
3. Betriebsvorschrift zur Trennung von Ortho- und Para-Nitrochlorbenzol (Dr. Kalkbreuner).
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7. Vorschrift zur Herstellung von Pentaöl bzw. Lucex-Puder.
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9. Vorschrift zur Fabrikation von Porofor 254 (Azohexahydrobenzoesäuredinitril).
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11. Schmiestoffzusatz. Produkt 891.
12. Vorschrift zur Fabrikation von "Atebrin".
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14. Prontalbin rein (Dr. Broeg).
15. Eleudronsalt. 2-(p-Aminobenzolsulfonamido)-thiazolnatrium (Sulfathiazolnatrium, 2 Sulfanilamidothiazolnatrium).
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17. Tanigau, extra A.
18. Fabrikationsvorschrift zur Aufbereitung von Sulfitabläuge (Dr. Goll).
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20. Tanigau extra B.
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22. Betriebsvorschrift Desmoder H = Hexamethyleudiisocyanat.
23. Betriebsvorschrift für Desmodur T (= Toluylendiisocyanat) Mol. 174.
24. Betriebsvorschrift zum Aufschmelzen von Desmodur T-Rückständen.
25. Betriebsvorschrift für Desmodur R.
26. Igamid U.
27. Vorschrift für Technikumsausätze von Igamid U (Pulverform).
28. Binde-Mittel 28 (Desmophen 900) = (Dr. Liese).
29. Bindemittel 28 HH (Desmophen 900 (Dr. Liese).
30. Desmodur und Desmophen als Lacksebstoffe.
31. Herstellung von Gasplanen aus Desmophen-Desmodur.
32. Lauseto neu (2509).
33. Laboratoriumsvorschrift zur Herstellung von M 2509.
34. Herstellung von p-Chlorbenzolsulfochlorid und Chlorbenzolsulfinsäure-natrium.
35. Wanzenmittel D 1210.
36. 3,4 Dichlorbenzylchlorid aus Orthodichlorbenzol, Paraformaldehyd und Salzsäure.
37. 3.4-Dichlorbenzylalkohol (Dr. Stroebe).
38. Lauseto-neu 2509 (Bayer).
39. Gebrauchsanweisung.-Wanzenmittel D 1210 (Bayer).

## APPENDIX I

### PREPARATION OF SONTOCHIN

#### Ethyl Ester Propionic Acid $\text{H}_3\text{CCH}_2\text{COOC}_2\text{H}_5$

1 liter pure  $\text{H}_2\text{SO}_4$  and 1 liter absolute alcohol are heated on the oil bath to  $150-160^\circ \text{C}$  in a 12-liter flask of porcelain with stirrer and cooler, and dropping apparatus. At this temperature during 5 hours thru the dropper is added a mixture of 12.5 liters of propionic acid and 12.5 liters absolute alcohol about at the rate of the distilled ester. The temperature is held constant.

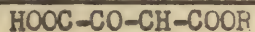
The raw distillate is washed in a separatory funnel with an equal amount of water, then made acid-free with cold 10% soda solution, and then with water. The ester is dried with  $\text{CaCl}_2$ , filtered, and distilled fractionally, BP<sub>D</sub>  $760^\circ$   $95-100^\circ$ .

According to the purity of the propionic acid there is a forerun of BP  $75-95^\circ$  which is washed a second time with water, dried and fractionated whereby a small portion of BP  $95-100^\circ$  is obtained.

Total yield 12.5 kg, i.e., 72%.

By use of specially pure propionic acid the yield is raised to 80%.

#### (1) Oxalylpropionic acid ester

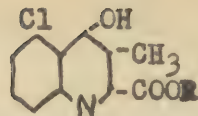
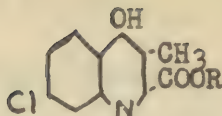
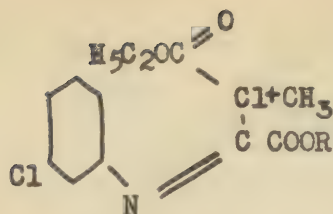


A mixture of 6 kg diethyl oxalate and 4.4 kg ethyl propionate is prepared of which 400 cc is reserved for beginning the reaction and the rest diluted with 9 liters benzol.

In a stirring vessel of porcelain of 25 liters capacity in an oil bath and with steam heating with a wide metal reflux cooler with a short glass connection and a dropping funnel, is added 1.2 liters hot benzol and 960 gms metallic sodium in equal slices of  $1/2$  cm thickness and decomposed with the 400 cc of ester mixture. Oil bath temperature at the beginning is held at  $80-90^\circ$ . After 20 minutes the reaction goes rapidly with production of hydrogen. If it slows up the ester mixture diluted with benzol is added to  $1-1/2$  hours thru the dropping funnel so that the benzol stays in lively boiling. During this time the steam heating is stopped. After all is in and the reaction slackens, it is stirred 1 hr at a bath temperature of  $80-90^\circ$  and a further hour without heating.

If after this time the sodium is decomposed the solution is poured still warm into 35 liters of water and 2.8 litres glacial acetic and stirred 10 minutes. The benzol solution is separated from the aqueous layer and the latter twice stirred with 7 litres benzol. The joined benzol solution are dried with  $\text{CaCl}_2$  and filtered. The benzol is distilled off under a little vacuum and the residue fractionated under high vacuum. BP<sub>4</sub>  $104^\circ$  Yield 5.8 - 6 kg.

#### (2) 3 Methyl - 4 oxy 7 - (5) chlorquinolin carbonic acid ester.



In an apparatus for continuous azeotropic distillation 4450 gm oxalyl propionic acid ester, 2800 gm m-chloraniline, 4 litres chloroform is decomposed with 7cc conc HCl and held at boiling until splitting off of the calculated amount of water (22 mol = 396 cc) in about 8-10 hours. Then the chloroform is distilled and the last residue removed in vacuum at water bath temperature. The Schiff's base remains behind as a reddish oil to be further worked up as a raw product.

70 litres oil (DAB<sub>2</sub>) is heated to 255°C in an iron stirring vessel with direct heating, cooler, thermometer, and dropping funnel. The Schiff's base is added thru the funnel inside of 30 minutes. The alcohol split off is distilled. After the addition the temperature is held 5 minutes, then the batch is cooled with stirring. The reaction product crystallizes at about 160° C, is filtered and washed twice with ligroin or benzol, and dried at 100°. The melting point of this isomer mixture is about 190°C.

### Separation of Isomers

#### Apparatus:

Porcelain stirring vessel in oil bath with steam heating, reflux condenser and inlet tube.

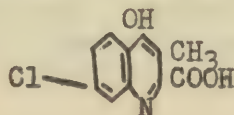
The isomer mixture is brought to boiling with 18 litres absolute alcohol and at the boiling temperature is led in 1 kg dry HCl gas during 3 hours, gradually bringing complete solution. With gradual cooling in 2 hours 1/2 kg HCl gas is led in whereby the hydrochloride of the 7 chlorquinoline compound crystallizes out, which is filtered off and washed once with 2.5 litres HCl - containing absolute alcohol and twice with pure absolute alcohol, and dried in air.

Yield 3110 gm, i.e., 47% on m-chloraniline.

FP of the HCl salt 196°, of the free ester 226°.

The alcoholic mother liquor contains the 5-chlor isomer and some 7; it is poured into 100 litres water, whereby the free ester separates out, which is filtered, washed with water, and dried at 100°C.

#### (3) 3-Methyl - 4 oxy 7 chlorquinolin 2 carbonic acid

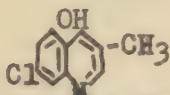


3110 gms ester hydrochloride are heated 2 hours under reflux in a stirring vessel with 15.5 litres 2N caustic soda solution, diluted with hot water to 40 litres and acidified with dil HCl. Product is filtered,

washed with water and dried at 100°C.

F 264° (CO<sub>2</sub>). Yield 2410 gms of 100%.

(4) 3-Methyl 4 oxy 7 chlorquinoline

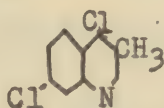


M: 193.5

10 litres paraffin oil is heated to 275° in a vessel of nickel of 15 litres capacity with stirrer, thermometer, wide exit tube, and closeable dropping funnel of sheet iron. Thru the funnel is added at this temperature 2.5 Kg 3 Methyl 4 oxy - 7 chlor - quinoline carbonic acid-2 in small portions during 20-30 minutes. The CO<sub>2</sub> split off goes thru the exit tube and led away by low vacuum from a water pump. Temperature is held 2-3 minutes and then the batch is cooled with stirring hastened by blowing air on the outside of the vessel. At 80° the oxy compound is filtered and washed three times with 2.5 litres ligroin and dried at 100°. F 334° Yield 1970 g, i.e., 97%.

The paraffin oil can be used 4-5 times and then purified with H<sub>2</sub>SO<sub>4</sub> and NaOH. Likewise the ligroin is recovered by distillation except the last charge which is used for the first wash for the next batch.

(5) 3 Methyl - 4,7 - dichlorquinolin



In a porcelain stirring vessel of 33 litres content in an oil bath with dropping funnel and reflux cooler 5 kg 3 methyl - 4 oxy - 7 - chlor-quinoline is decomposed with 15 litres dry chlorbenzol and heated in the oil bath at 170 C. 5.4 kg POCl<sub>3</sub> is added during 2 hours in small amounts, in the beginning about 50 cc and later for the last 800 cc at the rate of 100 cc at a time. After each addition the course of the reaction (lively boiling) is watched. During the addition the steam heating is not stopped; at the end the oil bath is heated for 3 hours and allowed to cool with stirring.

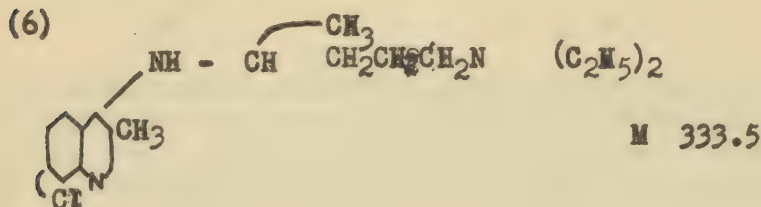
During the reaction HCL gas comes off at the beginning, in the second half it shows up as salt formation.

The cooled chlorbenzine solution and small amounts of crystallized reaction product are added in open vessel to 25 litres water and stirred 1/2 hour.

Then about 10 kg ice and 5 litres chlorbenzol recovered are added and at 20° ammonia is added to alkaline reaction (about 6 litres). The batch is stirred 15 minutes and allowed to stand 1 hour to separate the layers of which the lower contains the chlor compound dissolved in water which is added back to the aqueous layer and the whole extracted with 5 litres chlorbenzol. After separation and washing with water

this chlorbenzol is joined with the rest.

To determine melting point a test portion of chlor compound is distilled in vacuum after removal of chlorbenzene, BP<sub>2</sub> 140°, FF 90° yield 92%.



"SANTOCHIN" BASE - 3 Methyl - 4 - (5' diethylaminopentyl - 2' amino)-7-chlorquinoline.

The solution of 3 methyl - 4.7 - dichlorquinoline in chlorbenzol in a porcelain stirring kettle of 23 litres capacity on an oil bath with steam heating, with cooler and dripping funnel is freed of chlorbenzol under water pump vacuum and at about 100° bath temperature. Towards the end the temperature is raised to 140°. When the chlorbenzol is distilled off the apparatus is connected up to a reflux condenser.

Then 2 kg pyridine, 2.5 kg phenol and 2.5 gms NaI are added and temperature raised to 150 - 160° thru gas heating and thru the dropping funnel at this temperature is added over 3 hours 5.6 kg (1.5 mol) novoldiamine. Temperature is raised to 160 - 170° and left 15 hours with stirring.

After cooling the malt is diluted with 15 litres methylene chloride and 6.5 litres glacial acetic acid and 3.0 kg crystal sodium acetate in 15 litres water is added. After 5 minutes stirring the batch is allowed to stand 1/2 hour to separate. The methylene chloride layer which contains phenol and weakly basic parts is filtered. The methylene chloride is washed with 1 litre 10% acetic acid, which in turn is added to the chief fraction in the kettle.

In the same way the acetic solution is stirred up with 5 litres methylene chloride.

The purified acetic acid contains Sontochin and excess novoldiamine. It is covered over with 10 litres benzol, decomposed with ice and made strongly alkaline with 150 mols NaOH solution (too much NaOH causes milky precipitate) after 10 minutes stirring both layers are allowed to separate, the lower water layer sucked out and the benzol layer in which the Sontochin is again washed with 5% NaOH solution and twice with water. The benzol is distilled off with some vacuum and the residue fractionated under high vacuum.

BP<sub>2</sub> 210-220° Yield 61 kg, i.e., 77.6%.

## A P P E N D I X "2"

Therapy Test with Endochin 29 May 1941.

Siölli, F.

Endochin was administered to 5 febrile malaria patients.

For each patient an individual case history was kept including the fever curve.

The attempt at a temporary interruption of the attack with 3 times 0.1. Endochin on one day (case Hecht) was not successful.

Case of the patient Thyssen shows that the administration of 0.2 three times daily for 5 days (3.0 total) also had no effect.

The same was demonstrated by the patient Reinking with a 2-days administration of 3 times 0.3 and 1 single additional administration of 0.3 (total 2,1).

The same was shown in the case of the patient Gallo, who received 3 times 0.4 daily for a period of 6 days a total of 8.4

The case of Keller who had undergone a spontaneous interruption of the attack, shows that the dose administered in this period (3 times 0.3 Endochin for 5 days, i.e., 4.5 Endochin) did not prevent a recidivation after several days, with positive plasmodia findings and typical fever.

From this one may draw the conclusion that no effect is obtained in tertian malaria.

Urinalysis in the case Gallo, after the patient had received 3 times 0.4 Endochin for 3 days showed slight opalescence in the urine beginning 17 May; there were no findings in the urine of the others.

The author felt that he could not take the responsibility for a further increase in dosage.

## APPENDIX 3(a)

### Prophylaxis Test F. Sioli with Endochin 12 May 1941.

Beginning on 20 April, Endochin therapy tests had been performed on the febrile patients, Thyssen Hecht, and Keller. From these cases the conclusion was drawn that according to the plasmodium test and according to the fever Endochin has no therapeutic effect. Prophylaxis tests were begun on 7 May 1941.

It was planned to apply swarms of infected mosquitoes to a number of patients, and to treat one or several of these patients with Endochin prophylactically, while leaving one or several patients untreated.

The available swarm of mosquitoes consisted of 30 infected Anopheles, which had been infected 23 April 1941 by Thyssen (strain III Madagascar) and which had shown an abundance of stomach cysts since 28 April and salivary gland findings since 30 April 1941.

The first prophylaxis tests were begun on 7 May 41 with three patients.

Grosswöllenböcker,	Diagnosis	Schizophrenia
Bürgers, Leopold,	"	Schizophrenia
Jung, Leo,	"	Feeble-mindedness

Of these, Grosswöllenböcker and Bürgers received 3 times 0.1 Endochin daily, beginning 7 May 1941. No Endochin was administered to Jung. Anopheles were applied to all three 8 May 1941, of which

6 fed on Grosswöllenböcker

3 on Bürgers

2 on Jung.

Grosswöllenböcker and Bürgers received additional doses of 3 times 0.1 Endochin daily until 13 May 1941, i.e. each for 7 days.

A new series was begun on 13 May 1941, consisting of the patients:

Bandura,	Schizophrenia
Herrenbrück,	Schizophrenia

On 13 May Bandura received 3 times 0.1 Endochin and was to continue taking it during the entire period of incubation.

On 14 and 16 May the swarm with which the three others had been infected was applied to Bandura and Herrenbrück.

4 mosquitoes fed on Bandura

4 on Herrenbrück

28 May 1941.

First group (Grosswöllenböcker, Bürgers, and Jung):

Grosswöllenböcker had a febrile attack on 20 May 1941 (the 14th day) and the plasmodia findings became demonstrable from 21 May on. Fever and positive plasmodia findings persisted until the attack was stopped by other remedies.

In Bärgers, the plasmodia became evident on 21 May 1941, i.e. on the 15th day; the first distinct febrile attack took place on 23 May. Both continued until other remedies were applied.

In Jung the plasmodia test became positive on 26 May. Fever had not yet appeared at the time of the report, 28 May 1941.

The second group, Bandura and Herrenbrück, was not yet plasmodia-positive on 28 May, but Bandura had the first febrile attack on 27 May, i.e. on the 14th day, up to which day he had received Endochin.

From these tests one may draw the conclusion that in the above manner and quantity Endochin does not display a prophylactic effect.

It does not appear advisable to continue the prophylactic tests with larger doses, as, considering the length of time during which the doses were applied, especially in the case of Bandura, an effect of the quantity administered should have become evident.

## A P P E N D I X 3(b)

Diapromin-prophylaxis tests in malaria infection by mosquito and blood transmission. - F. Sioli.

Diapromin was first administered to patient No. 62/III. She had been infected by means of 10 anopheles. Diapromin was administered from the 8th to the 12th day after the infection, 0.1 daily, i.e., a total of 0.5 gm. The first febrile attack occurred on the 15th day after the infection, i.e., 4 days after the last dose of Diapromin; plasmodia were already found 2 days before. The period of incubation and the development of the plasmodia were not influenced by Diapromin.

After a discussion with Dr. Kikuth, the author administered a dosage of 3 times 0.1 gm Diapromin on the day before the infection, 3 times 0.1 gm on the day of infection, and 3 times 0.1 gm on the following 4 successive days. This treatment was administered to patients 3/IV, after mosquito infection, and 4/IV, after blood infection.

For a control, patient 2/IV was inoculated on the same day with the same anopheles, and patient 5/IV with the same blood. The time of incubation and the development of the plasmodia were not influenced by the Diapromin medication, neither in the case of the mosquito infection nor in the case of blood infection. The development of the mosquito infection and of the blood infection went through an exactly parallel course in those treated with Diapromin and in the untreated patients.

### Individual enumeration:

Case 2/IV without Diapromin infected on 8 June with 18 anopheles. 1st febrile attack 21 June.

Case 3/IV with Diapromin infected on 8 June with 15 anopheles. 1st febrile attack 21 June.

Abundant plasmodia findings in both cases on 21 June.

Case 5/IV blood inoculation on 10 June (without administration of Diapromin). 1st febrile attack 17 June.

Case 4/IV blood inoculation on 10 June (without administration of Diapromin). 1st febrile attack 23 June.

In both cases sufficient plasmodia findings on 21 June. The somewhat delayed incubation of the Diapromin-treated case lies within the customary limits of incubation and is not to be considered as an effect of Diapromin.

Summary: The Diapromin tests performed by the author so far have not shown any efficacy of the substance.

## A P P E N D I X 4

Report by Professor F. Sioli on the reactions and effects of Brachysan in the treatment of artificially induced benign tertian malaria of paralytics - 7 December 1944.

The experiments were begun in February, 1944. At first a dosage and period of treatment were given by which, if the Brachysan worked, a sterilizing effect was to be brought about--that is to say 3 x 0.1 gm Brachysan daily for a period of seven days. To illustrate the effects of this dosage charts No. 1(Ulrich), No. 2(Schmidt), No. 3 (Palupitschin), No. 4(Klatt), and No. 10(Weisemann) are given. These charts show that with daily dosage of 3 x 0.1 gm the fever drops at a regular rate and the plasmodia disappear.

In case No. 1(Ulrich) who at first had tertian and after the ninth paroxysm of fever quotidian rises, on 15/2/44 after the 11th attack, the treatment with Brachysan was begun. On the same day the daily rise of fever was very much reduced and passed rather more slowly; on the next day, the patient had high fever again, but from then on he was free of fever. On the second day of treatment the plasmodia had decreased. On the third day smears were only faintly positive, and plasmodia had disappeared on the fourth day.

Case No. 2(Schmidt) had 11 paroxysms of fever in unbroken daily sequence and showed a large number of plasmodia. He was given Brachysan on 18/2/44. On the 18th and 19th respectively he had attacks of fever, by the fourth day (21 Feb.) of treatment he had only isolated plasmodia, and from then on he was free both of fever and plasmodia.

Case No. 3(Palupitschin) (to which reference will be made again later). Since this man had already been given a small Brachysan dosage of 1 x 0.1 gm after the 8th attack (of the quotidian type) on 13/3/44 he was given the higher dosage. On the 13th and 15th he had paroxysms (that of the 15th being considerably milder); on the 14th he had fewer plasmodia. On the 15th there were only very few plasmodia and after that he was free of fever and plasmodia.

Case No. 4(Klatt) who had fever every third day and showed after the 7th paroxysm a large number of plasmodia, was given Brachysan on 5/2/44. He had slight fever again on 6/2. Already on 5/2 there was a decrease in the plasmodia and from 7/2 on he was free of fever and plasmodia.

Case No. 10 (Wiesemann) is included here because the patient suffered from naturally acquired relapsing malaria with daily fever and a large number of plasmodia. From 14/6/44 he was given Brachysan; on the 15th he had fever, but it was considerably abated and the quantity of plasmodia was considerably reduced. On the 16th only isolated plasmodia were present and after that he was free of fever and plasmodia.

From these first experiments the conclusion was drawn that this method of treatment with a daily dose of  $3 \times 0.1$  gm Brachysan over a period of seven days achieves a complete sterilization of the malaria; the fall both of the fever and of the number of plasmodia suggested that probably a three-day treatment with a daily dosage of  $3 \times 0.1$  gm Brachysan would result in sterilization.

This 3-day treatment was tried out on Case No. 8 (Posner). After the 10th daily paroxysm on 30/7/44, he received a  $3 \times 0.1$  gm Brachysan on two consecutive days,  $1 \times 0.1$  gm on the third and  $2 \times 0.1$  gm on the fourth; in all, therefore, 0.9 gm. He still had fever on the second day of treatment, 31/7/44, but after that he was free of fever. The plasmodia had decreased by the second day of treatment, by the fourth day there were only isolated instances and from then on tests were negative.

From this the conclusion was drawn that the 3-day treatment with a daily  $3 \times 0.1$  gm dosage of Brachysan resulted in the cure of B.T. and the next thing to do was to establish the minimum effective dosage.

Case No. 13 (Frau Meister) illustrates this experiment. She had quotidian fever (double tertian) and after the 6th paroxysm was given 0.5 gm of Brachysan on 26/10/44. She had one more attack on the 26th and from then on was free of fever. On the 27th only a few plasmodia were present, but after that tests were negative.

This case, therefore, proved the excellent effect of a further reduced dose.

Case No. 5 (Nauren) who had fever every third day was given, on 15/3/44 after the fourth paroxysm,  $3 \times 0.1$  gm Brachysan and on the following day  $1 \times 0.1$  gm Brachysan. The fever continued on the 16th-17th. The plasmodia decreased during these days, and from then on tests were negative. This was however only an interruption or temporary check of the disease; on 8/4/44, the 16th day after

treatment began, the smears again became positive and the tertian fever began again with the plasmodia varying from few to a fair number. There was then another 3-day interruption in the disease after which there were isolated bouts of fever as in chronic-malaria, until on 22-23/4/44 he was given 3 x 0.1 gm of Brachysan after which the fever disappeared. A small number of plasmodia remained until 4/5/44 when he was cured with atabrin.

This case leads to the conclusion that the dosage of 0.4 to 0.6 gm Brachysan does not result in final sterilization but only in a temporary cure.

The next thing was to discover whether this temporary cure was a consistent result of the lower dosage (0.4 gm) of Brachysan.

Several cases served this purpose:

Case No. 7(Arasin) had tertian malaria and after the 12th rise of fever on 28/8/44 was given 4 x 0.1 gm Brachysan in one day although the tests showed a fairly small number of plasmodia. On the 29th he no longer had any definite fever but merely a rather unstable temperature curve. After 11 days he had again high fever which after three paroxysms, in spite of the constant presence of plasmodia, disappeared spontaneously, then returned again after a further 5 days and after 3 attacks again disappeared spontaneously. Occasionally though, fever continued to reappear with only faintly positive smears. Thus he also reached a state of chronic malaria, which was finally checked on 21/10/44 with Atabrin.

Case No. 9(Zickies) with tertian fever, received 0.4 gm Brachysan after the 5th paroxysm of fever on 5/8/44. On the 6th he had one more rise of fever, but tests showed only very few plasmodia and from then on he was free of fever.

Case No. 11(Becker) had tertian fever and after the 10th attack on 12/9/44, during a period when there was a natural decrease of fever and while the low number of plasmodia remained unchanged, received on 19/9/44 4 x 0.1 gm Brachysan. There was no further fever and from the 21st on the plasmodia tests were negative.

Case No. 12(Frau Lohmar), with quotidian fever, received 2 x 0.2 gms Brachysan on 18/9/44. The fever continued unabated on the 19th and 20th and after that ceased

entirely. On the 20th the number of plasmodia had decreased, by the 21st there were only isolated instances and after that tests were negative. After 14 days a test on 4/10/44 again showed a small number of plasmodia and on the following day fever of the double tertian type returned. She was cured on 10/10/44 with Atabrin.

These experiments showed that although sometimes this dosage resulted in a final cure equally often the cure proved to be merely temporary so that the following conclusion is to be drawn:

A temporary cure is certain, but a final cure is not certain with this dosage.

Therefore, the effect of even smaller doses had to be determined.

To this end 3 patients received, on one day only, 3 x 0.1 gm Brachysan.

No. 6 (Meyr, Richard) had quotidian fever and on 16/4/44 after the 5th paroxysm received 3 x 0.1 gm. On the following day the fever ceased and the plasmodia count decreased, all parasites disappearing on the 18th. After 13 days, on 30/8/44, there was a recurrence of fever (though no plasmodia were found) which ceased spontaneously after four paroxysms. On 11/9/44 tests again showed a small number of plasmodia, on the 14th there was a recurrence of fever with an increase of plasmodia, so that on the 20th the disease was cured with Atabrin.

No. 7 (Arasin) (already mentioned in connection with a temporary check caused by 4 x 0.1 gm Brachysan) had already been given 3 x 0.1 gm Brachysan on 21/8/44 after the 8th paroxysm of quotidian fever. This dose had no effect on him as regards either fever or the number of plasmodia.

No. 14 (Frau Brinkmann) was given 3 x 0.1 gm Brachysan on 22/9/44 after the 6th paroxysm of quotidian fever. After that there was one further attack on 23/9/44 with a decreased number of plasmodia which, after the 25th, were only occasional and then ceased. After 13 days there was one day's fever followed on 7/10/44 by spontaneous cure. On 9/10/44 only occasional, but on 12/10/44 considerable numbers of plasmodia were found. On the 13th and 14th two paroxysms of fever occurred followed by spontaneous disappearance of fever and of plasmodia.

The conclusion to be drawn from this experiment with 3 x 0.1 gm Brachysan is that a temporary cure of 13 to 21 days may result, but in some cases there is no effect.

Case 3(Palupitschin) showed no effect, as regards either fever or quantity of plasmodia, from 1 x 0.1 gm Brachysan given on 9/3/44.

On the basis of these findings it can be assumed that Brachysan exercises an excellent effect more or less equivalent to that of atabrin and sontochin. With a dosage of 3 x 0.1 gm Brachysan on 7 consecutive days the sterilization of benign tertian malaria can be certainly effected. Most probably a shorter treatment is sufficient. The limit of the sterilization effect lies somewhere between 3 and 7 days treatment. Experiments on 4 and 5 day treatments are not available in greater quantities.

Treatment with less than 3 x 0.1 gm on two consecutive days results in a temporary cure which, in the case of dosages of 0.5 and 0.4 gm is of somewhat longer duration. With a dosage of 3 x 0.1 gm there may be a temporary cure, but there may also be no effect at all.

The dosage of 1 x 0.1 gm has definitely no effect. It has, however, still to be decided whether a dosage of 2 x 0.1 gm will produce a temporary cure or a change from quotidian to tertian fever.

Tolerance was always good and there was no indication that larger and as yet untried doses would have a toxic effect.

In conclusion, one may say that Brachysan is the equivalent of atabrin and sontochin.

## A P P E N D I X 5

I. G. Werk - Elberfeld

### Sontochin

Sontochin is the salt of a nitrogen-containing organic compound with an organic acid. It is a slightly yellowish crystalline powder of bitter taste, which is slightly soluble in water.

1 tablet contains 0.1 gm sontochin (active ingredients) (sontochin base).

### Pharmacological Data

Toxicity tests with the water-soluble hydrochloride of sontochin yielded the following results:

#### **Acute toxicity:**

Mouse, subcutaneously: 25-50 mg/kg without symptoms;  
75 mg/kg, dyspnea, but  
speedy recovery;  
100 mg/kg, the same symptoms-  
of 3 animals, one died;  
200-400 mg/kg, clonic  
convulsions; all animals  
died within a short time.

Rabbit, subcutaneously: 25 mg/kg tolerated without  
symptoms;  
at 50 mg/kg temporary con-  
vulsions appeared two hours  
later, but the animal re-  
covered rapidly.  
after 100 mg/kg the animal  
lay on its side 30 min.  
after the injection; irregu-  
lar, accelerated respiration,  
irregular pulse, isolated  
cramplike convulsions.  
After 45 min. slowly beginn-  
ing recovery, after 60 min.  
again normal posture, but  
still weak; on the follow-  
ing morning again lively.  
at 125 mg/kg spasms and  
trembling appeared 30 min.  
after injection, convulsions  
after 35 min., death occur-  
ed after 45 min.  
after 150 mg/kg death occur-  
ed with the same symptoms  
within 30 minutes.

Rabbit, intravenously: 10 mg/kg tolerated without symptoms;

at 20 mg/kg the animal was exhausted, but recovered again after 30 min.

at 25-30 mg/kg clonic convulsions appeared immediately after the injection and death occurred within a short time.

Rabbit, orally: 100-200 mg/kg were tolerated without special symptoms;

after 300 mg/kg the animal had died by the following morning;

at 400 mg/kg spasms appeared after 2 hours; at first the animal appeared to recover, but died by the following morning.

Guinea pig, orally: 50-300 mg/kg caused within 3 hrs. after ingestion a rise in temperature of up to 2.5°C, which had disappeared 7 hrs. later. There were no other symptoms of poisoning.

500 and 750 mg/kg caused within 2 hrs. a drop in temperature of 2° and lead into death without special concomitant symptoms.

Cat, subcutaneously: 5-10 mg/kg were tolerated well, without rise of body temperature. After 7 and 24 hrs., the blood contained no methemoglobin.

15 mg/kg caused after 5 hrs. a slight rise in temperature. The following morning the temperature was even higher, after 4 days the animal died, apparently from an intercurrent disease. After 6 and 24 hrs., the blood contained no methemoglobin.

20 mg/kg were well tolerated without effect upon the temperature and blood.

At 30 mg/kg there appeared a slight tendency toward a decrease in temperature, but there appeared no toxicity symptoms; the blood remained without methemoglobin.

After 40 mg/kg one cat died because of an intercurrent cause after 3 days.

50 mg/kg were tolerated well, without symptoms.

At 75-100 mg/kg the animal died after 30-70 min. with convulsions.

Cat, orally: 30-40 mg/kg were tolerated without any toxicity symptoms and without any effect upon the temperature. After 8 and 24 hrs. the blood was without methemoglobin.

after 50 mg/kg slight spasms and dilatation of the pupils appeared temporarily. Speedy recovery, no influence upon the temperature, after 7 and 24 hrs. no methemoglobin in the blood. The animal survived.

at 75 mg/kg soon after ingestion the following symptoms appeared: greatly dilated pupils, violent tremors, animal lying on its side, isolated spasms, very rapidly respiration, cyanosis. After 2 hrs. the animal had recovered somewhat; still slight tremors and dilated pupils. This state continued during the entire day. After feeding the temperature dropped 2° and in the course of 5 hrs. it rose again to its original value. After 7 and 24 hrs., there was no methemoglobin in the blood. The condition of the animal remained very low; it died after 3 days.

### Effect upon the blood pressure

In anesthetized rabbits doses of 2-10 mg/kg, administered intravenously, caused a short decrease in blood pressure with subsequent rapid recovery. At 10 mg/kg respiration was retarded temporarily. In the cat, 2 mg/kg intravenously also caused a slight lowering of respiration; 5 mg/kg caused rapid drop of blood pressure, cessation, and death.

2-10 mg/kg had a pronounced tonic effect upon the uterus of the anesthetized rabbit; in the small intestine there was a secondary increase of tonus simultaneous with the decrease in blood pressure. There was no influence upon the large intestine of the cat.

### Chronic experiments

Experiments with injections repeated daily in rabbits and cats showed that sontochin has only a very slight cumulative effect. Thus rabbits tolerated a daily administration of 15-20 mg/kg for a period of 30 days without essential disturbance of their condition. The only symptom was a slight decrease of the number of erythrocytes and of the hemoglobin value, which rapidly rose again to their original values upon discontinuation of the administration of the remedy. Cats also tolerated the 30-fold administration of 10-15 mg/kg; here too transitory anemia occurred.

The oral administration of the sontochin salt, available in tablet form, yielded a completely analogous effect as the subcutaneous injection of the hydrochloride. Based on active ingredients, the following were determined to be the smallest fatal doses:

Guinea pig:	Orally	0.5 gm/kg
Cat:	Orally	0.25 gm/kg
Rabbit:	Orally	0.25 gm/kg

## Chemotherapeutic data

After introductory experiments in which it was determined that sontochin must be considered to be a schizont remedy, the substance was subjected to a thorough investigation in comparison to atabrine.

With regard to the toxicity of sontochin in canaries, determined by means of Roehl's method of oral administration with a hollow probe, it was found that the fatal and the barely tolerated doses agree with those of atabrine: 1/50: fatal; 1/100: survived, if these doses were administered on 6 successive days.

The following doses were determined to be therapeutically effective in canaries infected with *Pr. praecox* = *P. relictum*: 1/1500 was effective, i.e., this dose, administered on 6 successive days delayed the appearance of the parasites for 12-14 days in comparison with the control animals. At a dosage of 1/3000 this effect was, as a rule, no longer evident. Thus these classical tests show a chemotherapeutic index of 1/15 in comparison to atabrine with 1/30.

Similar to atabrine, and in contrast to plasmochin, sontochin has no effect upon the gametocytes in the blood of *Haemoproteus*-infected rice finches.

The action of the substance is of special interest in the so-called combination test of simultaneous administration of plasmochin and sontochin in *Haemoproteus* infection of the rice finches. It is immaterial whether the combination of the remedies in question is simultaneous or whether the plasmochin treatment precedes the sontochin treatment. With the aid of this test the mechanics of the effect of atabrine were clarified and the substance was determined to be a schizont substance. In this method of testing it was shown that sontochin has an effect similar to that of atabrine. While with a dosage of 1/6000 plasmochin the gametocytes disappear after a short period, but reappear in all cases as a rule after 14 days, a complete cure may be attained if the tests are arranged in such a manner that 1/6000 plasmochin is administered for 4 days and 1/200 sontochin subsequently, likewise 4 times. From these results one must draw the hypothetical conclusion that simultaneous treatment with plasmochin and sontochin destroys the gametocytes in the blood by means of plasmochin and the schizonts in the endothelia by means of sontochin.

It must also be especially stressed that treatment with sontochin causes distinct degenerative changes in the parasites of bird malaria, especially a vacuolization which in a certain sense must be considered as the direct effect of the substance upon the parasites.

In summarizing it must be stated that the following chemotherapeutic effect of sontochin was observed:

1. The therapeutic effect of sontochin in bird malaria is similar to that of atabrine.
2. In bird malaria in Roehl's model test it has, however, a somewhat lower chemotherapeutic index than atabrine.
3. In absolute numbers sontochin is half as effective as atabrine.
4. Like atabrine, sontochin is primarily a schizont remedy.
5. In treatment with sontochin there occurs a degenerative change in the parasites, which allows one to conclude that there is a direct effect of the substance upon the parasites.
6. On the basis of the chemotherapeutic tests in bird malaria and in the Haemoproteus infection of the rice finches it appears suitable to test sontochin also as to its efficacy in human malaria.

### Application

On basis of the pharmacological results, one may expect sontochin to be tolerated in approximately the same doses as atabrine. It is proposed to consider the first group of tests only as an investigation of tolerance toward the substance; in this a dose of 0.1 gm three times daily is to be given for only 2 days, and after the harmless nature has been determined, this period is to be extended to 7 days. With this dosage one should expect an effect upon malaria. If the desired intensity is not reached with this quantity, an increase in dosage should be possible according to the pharmacological results. In this respect, careful attention should be paid to any possible secondary effects, especially symptoms of excitation, and the behavior of the blood aspect.

Wuppertal-Elberfeld, 29 December 1937.

## A P P E N D I X 6

Further developments in malaria therapy: Sontochin, a new synthetic malaria remedy (Walter Kikuth, Chemotherapeutisches Institut der I.G., Werk Wuppertal-Elberfeld)

The discovery of the two synthetic malaria remedies, plasmochin and atabrine, is doubtless the greatest advance of the last two decades in the field of malaria research. Entirely apart from the many new results and stimulations which sprang directly and indirectly from their application, the usefulness of these new remedies is of extraordinary significance for malaria prophylaxis and therapy. They not only rendered us independent from quinine, but in addition they possess a series of special advantages which now make it possible to combat malaria much more successfully than formerly. Even before the war atabrine and plasmochin were used with excellent success in amounts that increased from year to year. In the short period since these substances were developed, more than 2000 scientific articles have been published on the treatment of malaria with these synthetic substances. During the present war, however, their role--this holds true especially of atabrine, as quinine has almost completely disappeared from the world market--has become one that is almost decisive for the outcome of the war, for not only we, but also our enemies use this weapon almost exclusively in combatting malaria, and they produce it and use it in ever-increasing quantities. The advantages of atabrine are so evident and so generally recognized today that it is superfluous to discuss them at this point.

In spite of this great success, however, we have continued during the last few years to carry on intensive efforts to improve malaria therapy. With the means at our disposal and with the test methods worked out by us, we have recently examined a large number of new synthetic substances for their effect upon malaria. The result of this extensive systematic work is the discovery of a new malaria remedy, which is very similar to atabrine in its therapeutic properties, but which distinguishes itself from the latter by various advantages, so that one is justified in speaking of an advance in malaria therapy. This substance has been called, for the time being, Sontochin. The following section contains a short report on its chemotherapeutic characteristics.

Sontochin is a nitrogen-containing organic compound; for the present no data are to be presented on its structure.

The hydrochloride of this substance is an almost colorless crystalline powder, which is easily soluble in water and which has a bitter taste. Sontochin was prepared synthetically by Dr. Andersag, with collaboration of Drs. Breitner and Jung, in the Laboratory of Natural Sciences and Chemistry (Director: Dr. Schönhöfer) of the I.G.-Werk Wuppertal-Elberfeld; it was presented to the present author in May 1937 for the investigation of its chemotherapeutic properties.

The biological analysis of sontochin was conducted with those test methods which were at the author's disposal at the time of the development of atabrine, or which were worked out by the author and enabled him to distinguish in the laboratory the substances of plasmodium-like effect from those of an effect similar to that of quinine. These test methods were the model test for bird malaria worked out by Roehl and the model test for the Haemoproteus infection of the rice finch introduced by the present author to supplement the latter.

The technique of Roehl's test, which has been described several times elsewhere, is to be touched here only very briefly. Healthy female canaries are infected intramuscularly with plasmodia-containing blood (*P. relictum* or *P. cathemerium*) and they are treated on 6 successive days following the inoculation. The remedy, which is in solution, is administered to the birds orally by means of a hollow probe, so that they are not able to eject any considerable amounts of the administered substance. Thus this method permits a rather precise dosage. Whereas in the control animals parasites may be demonstrated microscopically regularly on the 5th day after infection, the blood of the birds treated with effective doses either remains entirely free or the plasmodia do not appear until much later.

Those animals which remained parasite-free may be successfully reinfected after some time, which indicates that the parasites were completely destroyed. In such a case one speaks of a chemotherapeutic "cure" (Permanent effect). If the parasites do not appear until the 10th day after inoculation, or later, this is designated as an "effect"; a shorter period of delay in the appearance of the plasmodia is considered a "trace effect".

Canaries have a somewhat smaller tolerance for stomachally administered sontochin than for atabrine. In absolute numbers the fatal and the barely tolerated doses are almost identical for both remedies. 1/100 sontochin (\*)

(\*)  $1/100 = 1/100$  gm per cc solution = 10 mg substance per cc.

$1/150 = 1/150$  gm per cc solution = 6.7 substance per cc. (1 cc is given for 20 gm of bird).

per 20 gm bird is the fatal dose;  $1/150$  per 20 gm bird is as a rule tolerated if the doses are administered daily for 6 days successively.

In the treatment of bird malaria in Roehl's test it is shown that sontochin is still effective in a dilution of  $1/1500$  (1 cc per 20 gm bird), while  $1/3000$  does not always show a full effect. Even at  $1/6000$  an effect upon the course of the infection is occasionally observed if one compares it with the control infection. The parasites, to be sure, can be detected from the first day of examination on, but they remain sparse and the disease has a much milder course. Now and then the birds tolerate a dose of  $1/100$ ; it is then often sufficient to cause a complete cure, so that they can be successfully reinfected a few weeks later. Table I presents a survey of the total results of such an experiment with the various dilutions of sontochin.

Table I

Dosage	Days after inoculation						Positive only on the	Reinfection
	5	6	7	8	9	10		
$1/100$	-	-	-	-	-	-	-	After 30 days, positive
$1/100$	(Intercurrent) died at very beginning						very	
$1/200$	-	-	-	-	-	-	19th day	
$1/200$	-	-	-	-	-	-	21st day	
$1/400$	-	-	-	-	-	-	17th day	
$1/400$	-	-	-	-	-	-	16th day	
$1/800$	-	-	-	-	-	-	16th day	
$1/800$	-	-	-	-	-	-	15th day	
$1/1500$	-	-	-	-	-	-	12th day	
$1/1500$	-	-	-	-	-	-	16th day	
$1/3000$	(*)	(*)	(*)	+	++			
$1/6000$	(*)	(*)	+	++	++			
$1/6000$	+	+	+	++				
control 1	+	++	+++	+++				
Control 2	+	++	+++	+++				

If one compares the absolute numbers of the effect of sontochin with those of atabrine, one finds that they almost agree, but atabrine appears to be somewhat more effective, since even with a dilution of  $1/3000$  there appears almost

in every case a distinct effect upon the parasites, while quinine, with an almost equal tolerance, shows an effect only to a maximum dilution of 1/400.

With the *Haemoproteus* infection of the rice finches we are dealing with blood parasites which in contrast to the plasmodia of human and bird malaria enter the peripheral circulatory system only in the form of sexually differentiated cells (gametes), whereas the non-sexual development and multiplication takes place in the endothelial cells of the inner organs, especially in the lungs and in the kidneys. In the living animal, therefore, only the female and male gametes can be demonstrated in the microscopic blood examination, while there is difficulty in finding the non-sexual forms, which is possible only by examining the inner organs. But even then they are found only with difficulty, especially if one is dealing with chronic infections, in which they occur only in sparse amounts. In latent infections apparently, the multiplication of the non-sexual forms in the endothelial cells, from which the gametes circulating in the blood originate, takes place only within narrow limits.

Artificial transmission of the blood infection from diseased to healthy birds, as is possible in the case of malaria, does not succeed in the case of *Haemoproteus* infection, as the gametes appearing in the blood are not able to multiply. Under natural conditions the disease is transmitted by the "louse fly", in which the gametes pass through the stages of development and multiplication. Breeding and keeping of louse flies in laboratory conditions, however, is an extremely difficult matter, and an experimental imitation of the natural transmission has not yet been successful in the case of rice finches. In chemotherapeutic tests, therefore, one uses only rice finches which have already been infected with *Haemoproteus* in the nest and in which this disease continues to exist in its chronic form. It is relatively easy to demonstrate the presence of such a latent infection by the presence of the gametes in the blood.

If latently infected rice finches in whose blood the gametes are present are treated with effective dosages of plasmochin, the sexually differentiated parasites will disappear within a few days. The blood remains free from parasites for a period of about 10-14 days, but after this period the gametes regularly reappear; they must have developed from the schizonts which were not influenced by the remedy.

In contrast to plasmochin, quinine and atabrine are entirely without effect upon the *Haemoproteus* gametes, and also upon the crescent forms of tropical malaria, even if they are administered in larger doses. Sontochin has exactly the same characteristics as quinine and atabrine. Likewise, this new malaria remedy is not capable of influencing the gametes of *Haemoproteus* in any manner. In order to furnish the proof for a schizont effect for sontochin, the author carried out a combined plasmochin-sontochin treatment for *Haemoproteus* infection, following his former experimental procedure. The results of this investigation are compiled in Table II.

Table II

Dosage	Before treatment	1	2	3	4	5	6	7	8	Recidivation within 14 days
Sontochin										
1/200	4 times	+	+	+	+	+	+	+	+	
1/400	6 times	+	+	+	+	+	+	+	+	
Plasmochin										
1/6000	4 times	+	-	-	-	-	-	-	-	on 13th day
1/12000	6 "	+	-	-	-	-	-	-	-	on 12th day
1/12000	6 "	+	-	-	-	-	-	-	-	on 13th day
Combination:										
Plasmochin										
1/6000	4 times	+	-	-	-	-	-	-	-	---
followed by										
Sontochin										
1/200	4 times	+	-	-	-	-	-	-	-	---
Plasmochin										
1/12000	6 times									
simult. with										
Sontochin										
1/400	6 times	+	-	-	-	-	-	-	-	---
Plasmochin										
1/12000	6 times									
simult. with										
Sontochin										
1/400	6 times									

The rice finches that had received sontochin in large doses of 1/200 and 1/400 for 4 or 6 successive days showed,

as was to be expected, no changes in the parasitary aspect of the blood. The number of gametes remained constant during a period of observation of two weeks. Plasmochin, administered in the dosage of 1/6000 4 times or in the dosage 1/12000 6 times successively, caused a temporary disappearance of the gametes from the circulatory system; they reappeared in decreased numbers, however, at the latest on the 13th day after the beginning of the treatment. In the combined treatment, in which sontochin was administered either subsequent to plasmochin, or simultaneously, the gametes did not reappear in the blood within the 2-week observation period. If one administers weaker doses, as was shown by other experiments, one may observe recidivations after a certain period; these, however, occur much later in comparison to the control animals.

From these results of the treatment of the *Haemoproteus* infection, the author was again able to draw the conclusion that sontochin has an effect upon the partition stages in the endothelia of the inner organs, thus preventing the formation of new gametes; in this sontochin corresponds to atabrine. In the treatment of human malaria this assumption proved to be correct inasmuch as sontochin proved to be effective predominantly toward the schizonts. From the causal-prophylactic point of view, sontochin is, however, just as ineffective as quinine or atabrine, as in the tests performed by the author sontochin had neither an effect upon the sporozoites nor upon the endothelial development stages of the bird plasmodia originating from them. Likewise it is impossible to prevent the flagella-formation of the gametes by means of sontochin, as is sometimes possible under special experimental conditions, with plasmochin. Sontochin is equally ineffective toward other blood protozoa, such as *piroplasma*, *trypanosoma*, and *leishmania*.

On basis of the author's chemotherapeutic results, sontochin was submitted by Hecht to a thorough pharmacological examination. The human organism has a great tolerance toward this substance; it had only a very slight cumulative effect.

Toward the end of 1937, Sioli received sontochin in order to examine it as to efficacy and tolerance in paralytics infected with tertian malaria. Sioli's investigations on therapy had such promising results that the preparation was transmitted in February 1939 for further tests on a wider base to Mühlens of the Hamburg Tropeninstitut, who performed his investigations in collaboration with Menk and Mohr.

In September 1939 the substance was transmitted to Rose and Sagel, and in 1942 Hauer and Fischer were asked by the H.S.I. to investigate the applicability of the new malaria remedy on the basis of their own therapeutic tests. Finally Schulemann (1942) was drawn into the H.S.I. for collaboration on the therapeutic tests.

In the meantime, experiences have been published covering several hundred patients. Expectations originating from the experimental work were completely fulfilled. Sontochin has proved to be a malaria remedy which in therapeutic respect is not inferior to atabrine, which excels by being well tolerated, and which has the great advantage of being colorless. Just like atabrine it is primarily a schizont remedy, i.e., it is without influence upon the gametes of tropical malaria. From the point of view of causal prophylaxis, sontochin is as ineffective as all other available malaria remedies, but on basis of its therapeutic characteristics successful clinical prophylaxis can be carried out with it as with atabrine.

#### Literature:

- W. Kikuth: Deutsche med. Wschr., 1932, 550; idem.,  
Zbtl.f. Bakteriologie, 1. Orig. 127,  
Beiheft 1-3, 172 (1932).  
Roehl: Arch. f. Schiffs - u. Tropenhyg. 30,  
Beiheft 3, 11 (1926).

## A P P E N D I X 7

Experiences with Sontochin as a curative and prophylactic agent in the treatment of malaria. (Manuscript of a report presented at the Hygienesektion 2. Arbeitstagung der beratenden Aerzte Ost, 3 Dec 1942) - Menk, W. (Direktor of the Clinical Section of the "Institut für Schiffs- und Tropenkrankheiten zu Hamburg" Direktor: Prof. Dr. Lührens).

After Kikuth had ascertained the efficacy of the new synthetic preparation, Sontochin, in the case of bird malaria, it was presented during the latter part of 1938 to the Hamburg Tropeninstitut for tests in the human organism. During the first few months of 1939 it was determined in cases of tertian malaria and in grave cases of tropical malaria that in all types of human malaria Sontochin had an effect similar to atabrine and quinine. With a suitable dosage and form of administration, Sontochin was in no wise inferior to these two schizont substances with regard to rapidity and reliability of the immediate clinical effect. Moreover, this substance possesses some advantages which especially stimulated detailed research. It is characterized by the fact that it is practically colorless, i.e., it does not possess the property of atabrine of causing a yellow discoloration of the skin with more intensive use. Moreover, in the form originally used by the author, which was later designated as Sontochin M, it lacks the bitter taste characteristic of quinine and also to a lesser degree of atabrine. Furthermore, the preparation is available for parenteral, intramuscular, and intravenous administration in 5% solution in sterile ampoules; under primitive working conditions and on trips and expeditions this is a considerable advantage, also from the point of view of saving space.

As soon as the usefulness of Sontochin was recognized, the author and his collaborators extended their field of observation. While the tests were continued in Hamburg, the author tested it during April and May 1939 in an intensely malaria-contaminated region of Cameroon in 65 cases, particularly in severe cases of malaria in native children and in colored workers who had recently migrated from the upper grasslands where malaria is not as prevalent, and who were affected very rapidly and very gravely with the disease in the coastal lowlands. As in Hamburg, the results were satisfactory. Intravenous administration proved to be especially effective. Exact tests on tolerance, on the behavior of blood bilirubin, urobilinogenuria, on the activity of liver and kidneys, the behavior of the heart and

the circulatory system, on the white and red blood picture, and the sedimentation reaction, and the check-up for methemoglobinemia possibly caused by the remedy showed no disadvantageous factors. In parenteral, especially intravenous administration, there appeared occasionally a lowering of the blood pressure, which was hardly worthy of mention, however, and was never dangerous. The tablets were well tolerated by the stomach and the intestines. Intoxication-like symptoms and other nervous symptoms to be ascribed with certainty to the substance were not observed, even with intravenous administration--in general not more than 0.2 was administered at one time--with the exception of a temporary feeling of heat or cold, and in one instance of slight vertigo. Although the data were already available at that time, they were not published at the beginning of the war because of certain agreements with the I.G. Farbenindustrie; and because of similar commitments, Sioli likewise did not publish his experiments performed with the substance. After extending their observations, Mühlens, Menk, and Mohr finally compiled in the spring of 1942 a preliminary report on 170 malaria cases which until then had been treated with Sontochin; among these were 84, in part very grave, infections with tropical malaria; this report was forwarded to the I.G. Farbenindustrie and in turn transmitted to the Heeres-Sanitätsinspektion (Surgeon General's Office, German Army).

This report also contained brief reports on 39 cases treated simultaneously with Sontochin and Plasmochin, and on prophylactic tests with Sontochin which had been begun by the present author and Dr. Steinbömer in late summer and autumn of 1941.

In the meantime the number of therapeutic observations had risen to a total of more than 425 cases of malaria treated with Sontochin.

The author's results were briefly as follows: 0.3 Sontochin - 0.6 gm Sontochin per day are well tolerated for a period of 5 - 7 days. The individual dosage never exceeded 0.3 gm, so that the maximum doses administered were in the form of 3 times 2 tablets daily or 2 times 3 tablets daily. Administered orally, 0.3 Sontochin per day does not have a sufficiently energetic and rapid effect in tropical and grave malaria, while this dosage suffices as a rule in lighter cases. Higher daily doses of 0.5 - 0.6 gm were at first administered only in grave cases, but later in general, for a period of 7 days. Noxious influences that could be ascribed with certainty to the remedy were not observed.

In grave cases, especially in tropical malaria, Sontochin is administered at first for several days parenterally, especially intramuscularly. In intramuscular administration, 0.3 is administered at one time. With a dosage of 0.4 at one time Dr. Steinbömer observed in non-German experimental persons several undesirable additional reactions (vertigo, vomiting). As a daily dose, 0.3 twice daily was tolerated in several cases for a period of 3 days without difficulty. 0.2 and 0.25 twice daily, and 0.3 plus 0.2 eight hours later were always well tolerated. In grave tropical malaria the author recommends higher dosage, as, for example, 0.25 twice daily, or 0.3 as the first dose and 0.2 as the second daily dose. In several cases treated in this manner, two daily intravenous injections of 0.2 and also one single daily dose of 0.3 were well tolerated. Slow injection, possibly diluted with NaCl; inject after thorough mixing with blood. The results of the initial parenteral treatment (3 days) were optimal even in cases of grave tropical malaria.

Nor does one fatal case, observed in a case of very grave tropical malaria in spite of Sontochin treatment, alter this favorable aspect. This was a very severe case of tropical malaria which after an alleged 3 days of atebriin-tablet treatment in another hospital, had been transferred to the author's hospital. In spite of very careful therapy of the circulatory system, and the administration of 0.3 Sontochin intramuscularly, 0.2 orally, and an additional 0.15 Sontochin intravenously 4 hours before death, this patient died about 12 hrs. after admission to the hospital with symptoms of acute heart failure. Since the autopsy revealed, besides the usual pathological changes due to fatal tropical malaria, a pronounced hemorrhage of the right adrenal, this case with its fatal course due to septicemic-cardial-suprarenal causation should be included among those cases, which, as they receive energetic treatment too late, are no longer to be cured by chemotherapeutic measures of any sort.

The parenteral treatment lasting 3 days was generally followed by 4 days of oral therapy.

Of the 3 Sontochin preparations examined for oral administration, the author gives preference to the Sontochin-R tablets, in spite of their bitter taste, because this modification is absorbed more rapidly than Sontochin-M. In the comparative tests performed by the author--which, however, were not very extensive and which were conducted only on mild to moderately severe cases of tertian malaria--with Sontochin-C dragees and Sontochin-R, the effect of the dragees did not appear to be less; nevertheless, the author does not favor dragees as they disintegrate too slowly.

Except in a few individual cases, the subsequent plasmo-  
mochin treatment was generally administered in the dosage  
customary after atabrine treatment. The author tested 104  
cases with simultaneous Sontochin-plasmo- treatment.  
With 0.03 plasmo- in addition to Sontochin, there were  
individual complaints of gastric disturbances; in one case  
of this group methemoglobinemia was observed. 0.02 plas-  
mochin and 0.015 plasmo- daily with 0.3 or 0.6 Sontochin  
seemed, however, to be well tolerated for a period of 5-7  
days. For certain reasons nothing may as yet be stated  
in regard to the frequency of recidivations after such  
combined cures. They also occur after the administration  
of higher dosages.

The author is of the opinion that Sontochin is a new  
schizontocidal malaria remedy of good immediate clinical  
efficacy for tropical-tertian, quartan, and oval infections,  
which at present, however, especially in grave cases, is  
administered in a weight dosage that is about  $1\frac{1}{2}$  - 2 times  
as high as that of atabrine. It is suitable for oral,  
intramuscular, and intravenous application. However,  
further experimentation as to the most suitable dosage and  
course of treatment still appears desirable before the sub-  
stance is released for general use, since it presumably is  
not ready to be administered by any physician in place of  
atabrine. Special attention must be paid to the treatment  
of very grave malaria by means of Sontochin and Sontochin  
plus atabrine.

There is no urgent necessity of introducing Sontochin  
into the treatment of acute febrile malaria, as atabrine  
and quinine are available as effective schizontocides;  
nevertheless it appears desirable to introduce it into  
therapy of cases that had frequent recidivations in spite  
of atabrine therapy, so that the treatment is not limited  
to atabrine alone, especially as one may assume that the  
effect and the point of departure of Sontochin are not  
entirely the same as those of atabrine. In regard to the  
possibility of chemo-prophylaxis by means of Sontochin it  
must be mentioned that 0.05 Sontochin-M per diem is not  
sufficiently certain in its effect; on the other hand 0.1  
Sontochin daily seems to be a suitable dosage as was  
demonstrated by repeated experiments with artificial  
(mosquito) infections with tropical and tertian malaria,  
which the author has performed for more than one year in  
collaboration with Steinbömer. Special value should be  
attached to a substance that does not have a bitter taste  
in case of prophylactic treatment extending over a longer  
period of time. Also here the present, limited experiences

do not justify a general application; also in this regard practical experiments of larger scope and with thorough control should be performed in the intense malaria foci occurring in the coming summer and autumn. It is also to be considered for intensified malaria prophylaxis; in this respect too more extensive practical investigations are recommended for the next malaria season.

## A P P E N D I X 8

Preliminary Report: Experimental investigations on Sontochin prophylaxis in mosquito-transmitted tertian and tropical malaria. (W. Menk and A. Steinbömer, Institut für Schiffs- und Tropenkrankheiten (Direktor Prof. Dr. Mühlens) and Heil- und Pflegeanstalt Langenhorn (Direktor Prof. Dr. Koertke)).

A certain disadvantage in chemoprophylaxis with atabrine and quinine is the bitter taste of the tablets prepared from these remedies. Atabrine is in itself more reliably effective, but it has the undesirable property of causing a more or less pronounced yellow discoloration of the skin upon longer administration. Prophylactic experiments with sontochin which in tablet form is practically tasteless and which, like the other sontochin preparations, causes no discoloration of the skin, seemed therefore of considerable interest in view of the excellent tolerance of the organism toward the substance.

In spite of the somewhat complicated arrangement of the tests, the authors began approximately 1-1/3 years ago to test the chemoprophylactic efficacy of sontochin-M in mosquito-transmitted tertian and tropical malaria. Expanding gradually, the tests were continued until now and have not yet been concluded. The daily dosage was 0.05 and 0.1 gm sontochin-M (in tablet form), which was administered every day to the adult experimental persons.

In order to create experimental conditions corresponding to the natural conditions of a continuous prophylaxis in an endemic region, the authors did not limit themselves to infecting the experimental persons only once, but in the course of time they reinfected them as far as possible with various strains of the two types of malaria from time to time, so that the patients longest under observation were infected up to 8 times. In the same manner chemoprophylaxis, which was begun on the day after the first infection, was continued without interruption up to the present in order to examine the tolerance toward a continuous prophylaxis, and chemoprophylaxis is to be continued, if possible, for 2 to 3 years with the same persons.

The advantages of such experimental investigations are obvious, as the number and type of the infections are known precisely, the administration of the remedies takes place under continuous control, and current blood and clinical

tests permit careful supervision; while observations on chemoprophylaxis under natural conditions of infection are often subject to the disturbing effect of numerous interferences which are difficult to eliminate.

The disadvantages of such experiments consist of the fact that one may perform them with only a relatively small number of persons, and that traumatic influences, such as exertions, want, injuries, non-specific infections (colds, intestinal catarrhs) which are known to favor malaria attacks in individuals practicing prophylaxis, are eliminated to a large degree in experimental persons receiving stationary treatment. The results found in such experimental investigations must thus be evaluated with certain reservations, but they nevertheless allow one with relative certainty to draw conclusions as to which dosage is too small for practice and which form of prophylactic treatment merits choice as a basis for practical chemoprophylaxis.

The number of persons used by the authors totalled 26, including the 3 control persons who received no prophylactic treatment up to the time of the first infection; among them 13 received only tropical malaria (M.T.), 6 tropical and tertian malaria, and 7 only tertian malaria infections. A total of 86 mosquito transmissions were performed.

The infections were undertaken with a total of 6 strains of tropical malaria (all, with the exception of one South American strain, of South or East European origin) and a total of 12 strains of tertian malaria (all of European origin). The strains were transmitted from untreated patients to mosquitoes and used for the infections as a rule only in the original passage. The mosquitoes, the adequacy of whose infection index had in each case been determined microscopically beforehand, were applied in small cages which in most cases contained 15 - 20 mosquitoes per person and infection.

The results of these experiments are compiled in Tables I and II. Table I shows the first 3 prophylaxis experiments with 0.05 and 0.1 Sontochin-M daily, at first in tropical malaria infections; in the course of the observations which by this time have lasted for about 1 year the patients received in the majority of cases pure infections of tropical or tertian malaria (up to a total of 8 infections). It is of interest and of special importance in regard to the practical significance of chemoprophylaxis that the 3 control persons who had not received prophylactic treatment were all

affected with grave febrile primary attacks of tropical malaria, with normal incubation period.

Chemoprophylaxis with 0.05 daily failed in 1 out of 4 cases, while in 3 cases with 0.1 daily there appeared no symptoms of disease nor positive blood findings.

Table II compiles the total results with persons who had been observed for periods of at least 3 months. Untreated control persons were no longer included in the series.

Also in a total survey it is evident that 0.05 daily does not suffice in practice. Besides the tropical malaria case in Table I, in which it was doubtful whether or not the patient had deceived the nurse as regards the regular ingestion of the remedy, this dosage also failed in 2 additional cases of a total of 10, once with tropical and once with tertian malaria. In 8 cases that received 0.1 daily there was no failure. An additional group of 5 cases under observation for only about 4 weeks (2 treated with 0.05, and 3 with 0.1 daily), in which no disturbances have appeared until now, have not been included in the tables.

**Summary:** Experimental investigations with mosquito-transmitted tropical and tertian malaria have shown that prophylactic treatment with 0.05 sontochin-M daily failed in 3 out of 10 cases; no failures occurred with administration of 0.1 sontochin-M daily in 8 cases, despite repeated infection, in observations lasting from 3 to 16 months.

15 November 1942.

**TABLE I**  
**Experimental malaria-prophylaxis investigations with Sontochin-M (0.05 or 0.1 daily)**  
 in mosquito-transmitted tropical malaria. Period of observation approx. 1 year.

Test No.	Prophylaxis	Mal. Attacks	Treatment	Reinfection	Course
1	Control with- out prophyla- xis	++ after 12 days	0.1 quin., 1.5 so. 5 days, then 10 days 0.05 so. daily	----	No fever after- wards
No.1 St. Trop. I Infection 10 Oct. 1941	4 0.05 sontoch. xis	++ after 16 days	2.9 so. in 8 days intram. & oral, then 3 wks. 0.1 and 12 wks, 0.05 daily.	----	- - -
7	0.1 sontoch.	0	always 0.1 daily	tert. VI. X. XII	Patient re-
3	Control with- out prophyla- xis	++ after 11 days	so. 1.8 in 7 days intram. & orally	-21 Aug. 42	mains healthy
No.2 St. Trop. II Infection 19 Dec. 1941	12 0.05 sontoch. xis	0	always 0.05 daily	+ trop. III 9 Jan. 42	Patient re- mains healthy
2	Control with- out prophyla- xis	++ after 8 days	2.4 so. in 7 days intram. & orally	----	No fever afterwards
No.3 St. Trop. III Infection 19 Dec. 1941	5 0.05 sontoch. xis	0	always 0.05 so. daily	+ trop. II, tert. VIII, IX, X until 21 Aug. 42.	Patient re- mains healthy
6	0.05 sontoch.	0	always 0.05 so.	+ tert. VI, VII, VIII (2 times) 21 Aug. 42	Patient re-
8	0.1 sontoch.	0	always 0.1 sont. daily	+ trop. II, Tert. VI 2 times, VIII, IX, trop. V 2 times - 25 Oct 42	mains healthy
9	0.1 sontoch.	0	always 0.1 sont. daily	+ trop. III 2 times tert. VI, VIII, IX, XI 2 times - 25 Oct. 42.	Patient re- mains healthy

TABLE II  
Experimental malaria-prophylaxis with soutochin-M (0.05 or 0.1 daily)  
 Period of observation: 3-16 months.

Number of infected experimental persons      Type of prophylaxis      Course: Patients remained healthy      Patients infected with trop.:tert.:      Results

3	Untreated controls	Ø	3	Ø	Normal first infection with trop.malaria
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3 (1: 3 times)	4 (trop.2: once) 2: twice) tert.2:3 times 2:4 times	0.05 so.-M daily	1	2	Ø	In 10 cases treated with 0.05 so.-M, 3 failures; among those 2 of 7 infected with trop. malaria
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	3 (3:3 times)	"	3	Ø	Ø	
--	---------------	---	---	---	---	--

2 (2: twice)		0.1 so.-M daily	2	Ø	Ø	In 8 cases treated with 0.1 so. M daily, there were no failures.
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2 (trop. 1:4 times) 1:3 times) (tert. 1:4 times) 1:5 times)		"	2	Ø	Ø	{
--	--	---	---	---	---	---

4 (3;3 times)	"	4	Ø	Ø	Ø	{
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## APPENDIX 9

Further experimental investigations on malaria prophylaxis by means of Sontochin-M (W. Menk and A. Steinbömer) (Addenda to the article "Experimental investigations on sontochin prophylaxis in mosquito-transmitted tertian and tropical malaria" by Prof. W. Menk and Dr. A. Steinbömer (1942)).

The number of persons participating in the experiments mentioned in the above article has been increased in the meantime to 31. The number of artificially caused mosquito infections was increased by a total of 14, consisting of 4 cases of tertian and 10 cases of tropical malaria infections.

This group also confirmed that the daily dosage of 0.05 sontochin-M was too small. 14 persons who were kept with a daily dosage of 0.05 sontochin have yielded in the meantime a total of 6 failures of the prophylactic treatment; among them, however, there were 4 cases of non-clinical (i.e., only blood-positive) malaria. The 2 clinical failures were cases of tropical malaria which had been mentioned in the table of the previous article.

On the other hand, 0.1 sontochin daily gives relatively reliable protection. In 12 cases which received such prophylaxis for a period of 13 to 25 months, there was not a single failure. Continued prophylaxis with 0.1 daily was always well tolerated; moreover, sensitive patients take this remedy willingly. Five of the cases mentioned received the substance for over 1 year, 7 cases for practically 2 years. With regard to the dosage it must also be mentioned that the weight of the experimental persons in the prophylaxis test ranged from 47.5 to 65.3 kg; average weight 53.6 kg (calculated for persons of 75 kg, the equivalent quantity of sontochin would amount to 0.14 per diem). It must also be mentioned that in 4 untreated control persons who had developed grave tropical malaria (M.T.), an apparently radical and primary cure was attained by means of sontochin treatment with 1.8 - 3.8 gm. Two of these cases remained under observation afterwards for 19 months, and 2 for 8 months after completion of the sontochin treatment, but no malaria symptoms of any sort had appeared.

### Prophylaxis with intensive infections in series

While in the above experiments one is generally dealing with infections repeated at intervals of several weeks, plans were made to perform tests in 1943 with very intensive mosquito infections (daily infections by 20 - 25 infected mosquitoes each, for 3 weeks).

Because of the major catastrophe, however, it was impossible to perform these experiments on a larger scale. Consequently, intensive infection was carried out only on 2 persons who had received prophylaxis with 0.1 sontochin daily. It is a striking fact that both persons had febrile attacks, 9 and 10 days respectively, after the first infection, lasting 1-1/2 to 3 days; however, the blood did not become parasite-positive. These febrile temperatures disappeared again, although the sontochin dosage was not increased, i.e., it remained constantly at 0.1 gm sontochin-M daily, nor did they recur in an additional 7 months of continuous sontochin prophylaxis. The blood also remained permanently malaria-negative during these 7 months of prophylaxis. Several weeks after the medication had been interrupted, there appeared in both persons tertian malaria with positive blood reaction (in one case 2 weeks, in the other 4 weeks after interruption of the prophylaxis). The weight of both patients was 56 kg. In both cases the infection was performed with 5 different strains of tertian malaria.

#### Prophylaxis in blood-transmitted malaria

Since the major catastrophe destroyed the mosquito-cultures of the Institute, the sontochin-prophylaxis tests were extended to persons who had been infected by means of blood-inoculations. In 7 cases of this sort (3 cases of triple tertian infection, 2 cases of double tertian and single tropical malaria (M.T.) infections, 1 case of one tertian infection, 1 case of 4-fold tertian and 1 tropical infection) the results in the course of 4 months of observation were unequivocal; there was no fever, nor parasite-positive findings, whereas the untreated controls had the typical course of the disease. Also in these 7 cases the infections were isolated, ranging in intervals from 1 week to 2 months.

Summary: In persons weighing about 54 kg, 0.1 sontochin-M daily furnishes reliable protection against malaria infections which are not repeated too frequently. Conditions in cases of very intensive daily infections require further investigations; but in this regard too the protective effect appeared remarkably good as shown in tests performed with 2 persons.

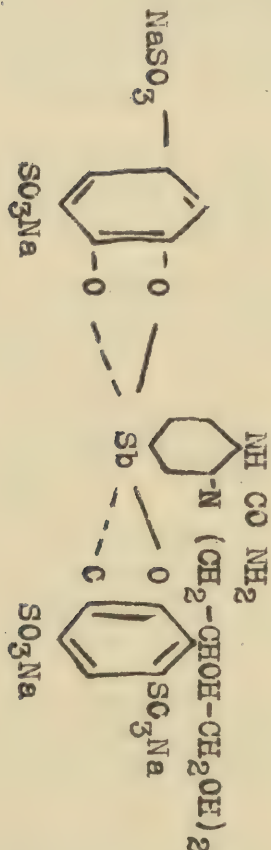
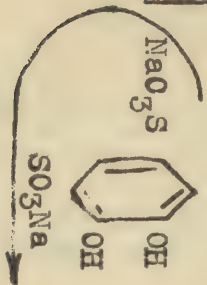
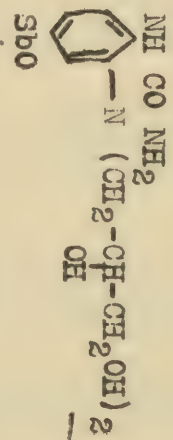
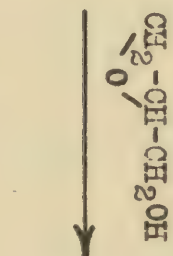
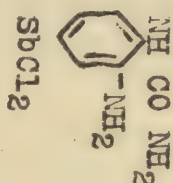
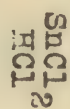
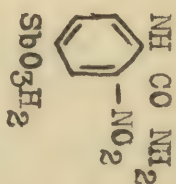
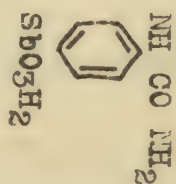
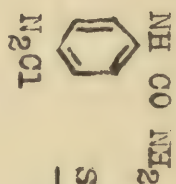
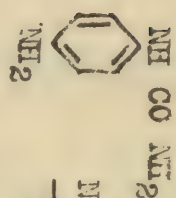
## A P P E N D I X 10

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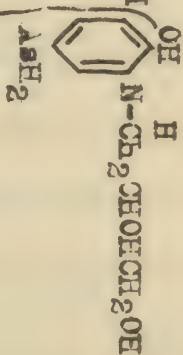
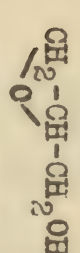
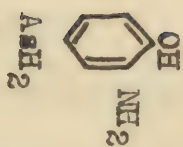
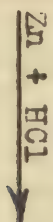
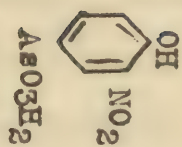
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1. H. Mauss and F. Mietzsch: Atebrin, ein neues Heilmittel gegen Malaria, Klin. Wchuschr. 12:1276-8, 1933.
2. F. Mietzsch and H. Mauss: Gegen Malaria wirksame Acridinverbindungen, Angewandte Chemie 47: 633-636, 1934.
3. Walter Kikuth: Zur Weiterentwicklung der Chemotherapie der Malaria. "Certuna" - ein neues Gametenmittel, Klin. Wchuschr. 17:524-527, 1938.
4. W. Kikuth and L. Mudrow: Malariaübertragungsversuche mit Blut und Organen sporozoiteninfizierter Kanarienvögel, Rivista di Malarologia 17 (Sez. I):1-14, 1938.
5. Walter Kikuth and Lilly Mudrow: Frühstadien der Vogelmalariaparasiten nach Sporozoiten infektion, Klin. Wchuschr. 18: 1443-1444, 1939.
6. Walter Kikuth: Die Chemotherapie der Malaria auf Grund neuer parasitologischer Erkenntnisse, Münch. med. Wchuschr. Uv. 10:362, 1939.
7. Walter Kikuth and Lilly Mudrow: Die Entwicklung der Sporozoiten von Plasmodium cathemerium im Kanarienvogel, Zentralbl. f. Bakt., Parasitenk. u. Infektionskr. 145 (I. Abteilung. Originale): 81-88, 1939.
8. W. Kikuth and L. Mudrow: Die Umwandlung der Sporozoiten in die endotheliale Phase der Malariaparasiten, Rivista di Malarologia 19 (Sez.I): 1-15, 1940.
9. W. Kikuth: Die Bedeutung des neuen Entwicklungszyklus der Malariaparasiten für die weitere Entwicklung der Malariatherapie, Deutsche Tropenmed. Zeitschrift 45: 138-142, 1941.
10. W. Kikuth: 25 Jahre deutsche Tropenheilmittel, Die Pharmazeutische Industrie 9:325-329, 1942.
11. W. Kikuth: Zur Frage der Malariaprophylaxe, Hoppe-Seyler's Zeitschrift f. physiol. Chemie 274: 9-18, 1942.

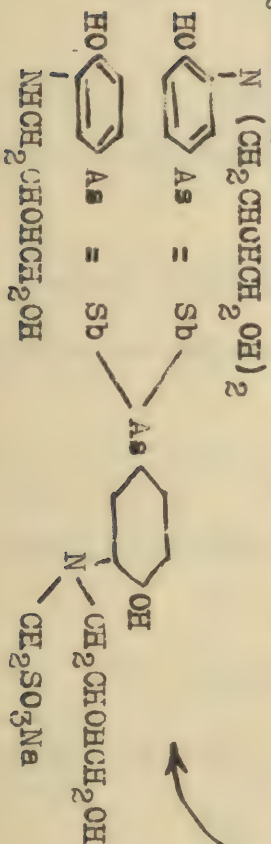
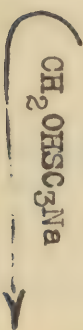
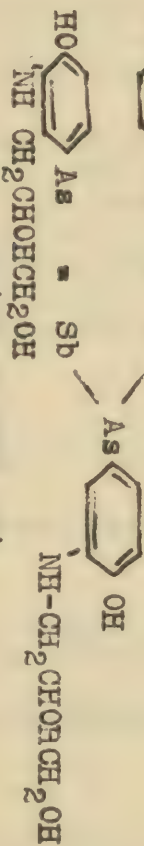
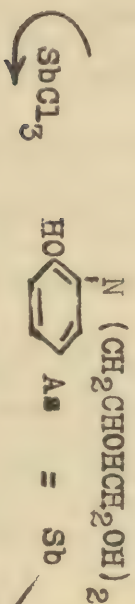
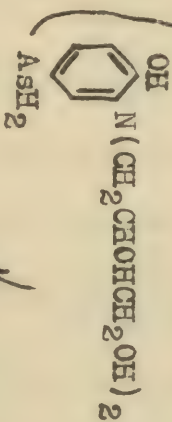
12. L. Mudrow: Über die Entwicklung der Sporozoiten bei verschiedenen Vogelmalariaarten, Rivista di Malarologia 21: 3-20, 1942.
13. L. Mudrow: Zur Sporozoitenentwicklung verschiedener Vogelmalariaarten 21:382-385, 1942.
14. Walter Kikuth: Die Malaria, in: Max Gundel (ed.): Die ansteckenden Krankheiten, 32d Ed., Leipzig, Georg Thieme Verlag, 1944.
15. W. Kikuth and W. Menk: Die Chemotherapie der Malaria, 2nd Ed., Leipzig, Verlag von S. Hirzel, 1944.



PREPARATION OF NO. 386B



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## APPENDIX 13

### DATA REQUIRED TO STANDARDIZE KIKUTH'S TESTING METHODS

#### I. Quinine Dihydrochloride. (Dosages in terms of salt).

Canary Toxicity = 1/50 dead, 1/100 living.

Blood-induced Canary Malaria = 1/100 - 1/400 Temporary Cure.

1/800 Slight Effect. 1/1500 No Action.

Sporozoite-induced Canary Malaria = 1/100 No Action

Hemoproteus Infection = 1/100 No Action.

#### II. ATEBRIN. (Dosages in terms of base)

Canary Toxicity = 1/50 dead, 1/100 living.

Blood-induced Canary Malaria = 1/100 - 1/3000 Temporary Cure.

1/6000 No Action.

Sporozoite-induced Canary Malaria = 1/200 No Action

(Symptomatic Effect of slight degree due to retained  
drug)

Hemoprotein Infection = 1/200 No Action.

#### III. PLASMOCHIN. (Dosages in terms of equivalent weight of mono- hydrochloride salt)

Canary Toxicity = 1/800 dead, 1/1500 living.

Blood induced Canary Malaria = 1/1500 - 1.50,000 Temporary  
Cure.

1/100,000 No Action.

Sporozoite-induced Canary Malaria = 1/1500 - 1/3000 Temporary  
Cure to Slight Effect.

Hemoprotein Infection = 1/3000 - 1/50,000 Temporary Cure.

1/100,000 No Action.

Exflagellation Test = 1/25,000 Temporary Cure. 1/50,000  
No Action.

# A P P E N D I X 14

Bemural, a compound with the formula:



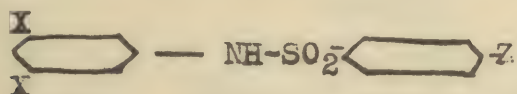
has the following physiological properties.

Toxicity: Per 20 g. of bird, 1/100 dead, 1/200 living.




Effectiveness: In malaria with Roehl's test, 1/1500 effective, 1/3000 no action.

in malaria prophylaxis test 1/800 effective.

Bemural is the most effective of all similarly constructed compounds. Variations in the structure of the molecule all produced less effective substances. Characteristic and especially important is the substitution of halogens in the 3,5 position. A change in this position produces ineffectiveness. The following table shows in detail the dependence of activity on the type of substitution:



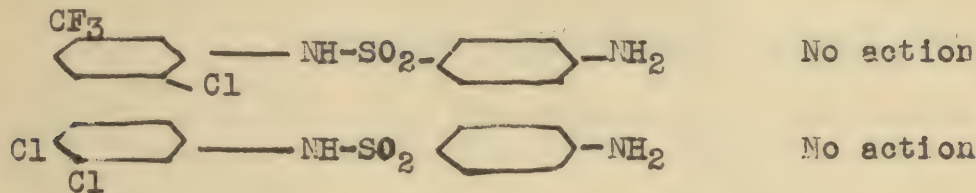
								(*)
X	Y	Z	Be	Pa	Toxicity (Bird)	Roehl's Test	Prophylactic Test	
Br	Br	NH <sub>2</sub>	768	5351	1/100 t	1/1500 W	1/800 W.	
(Bemural)					1/200 l	1/3000 o.W.		
Cl	Cl	NH <sub>2</sub>	745	5277	1/200 t	1/800 W	1/800 etwas	
					1/400 l	1/1500 o.W.	Wirk.	
J	J	NH <sub>2</sub>	704	5008	1/50 t	1/100 W.	1/200 W.	
					1/100 l	1/200 etw.W.		
CF <sub>3</sub>	CF <sub>3</sub>	NH <sub>2</sub>	802	5565	1/200 t	1/800 W.	1/400 etwas	
					1/400 l	1/1500 o.W.	1/800' Wirk.	
CH <sub>3</sub>	CH <sub>3</sub>	NH <sub>2</sub>	746	5278	1/25 l	ohneWirk.	ohneWirk.	
Br	H	NH <sub>2</sub>	789	5470	1/100 t	ohneWirk.	ohneWirk.	
					1/200 l			
CH <sub>3</sub>	H	NH <sub>2</sub>	785	5467	1/35 t	ohneWirk.	ohneWirk.	
					1/50 l			
Cl	Cl	NHCOCH <sub>3</sub>	743	5275	1/25 t	1/100 W.	1/50 etwas	
					1/50 l	1/200 o.W.	Wirk.	
Br	Br	NHCOCH <sub>3</sub>	761	5346	1/15 t	1/25 etw.W.	1/25 "	
					1/25 l	1/50 o.W.	1/50 o.W.	

X	Y	Z	Be	Pa	Toxicity (Bird)	Roehl's Test	Prophy- lactic Test
J	J	NHCOCH <sub>3</sub>	776	5408	1/10 t 1/25 l	1/25 W. 1/100etw.W. Wirk.	1/50etw.
CF <sub>3</sub>	CF <sub>3</sub>	NHCOCH <sub>3</sub>	765	5348	1/100 t 1/200 l	1/800 W. 1/1500etw.W. Wirk.	1/400etw.
CF <sub>3</sub>	CF <sub>3</sub>	NHCOC <sub>2</sub> H <sub>5</sub>	837	5889	1/25 t 1/50 l	1/50 W. 1/100etw.W. Wirk.	1/50 etw.
Cl	Cl	NHCCOC <sub>2</sub> H <sub>5</sub>	806	5568	1/25 t 1/50 l	ohne Wirk. 1/50etw.	1/50etw. Wirk.
CF <sub>3</sub>	CF <sub>3</sub>	NHCOCH <sub>2</sub> - SO <sub>3</sub> H	842	5914	1/10 t 1/25 l	1/25etw.W. 1/50etw.	1/50etw.
Cl	Cl	N-CH <sub>3</sub>   CH <sub>3</sub>	828	5814	1/50 t 1/100 l	1/100 W. 1/200o.W.	1/100etw. Wirk.
Cl	Cl	N=CH-  -OCH <sub>3</sub>	831	5817	1/25 t 1/50 l	1/50 etw. 1/100Wirk.	1/50 etw. Wirk.
Cl	Cl	N=CH- 	829	5815	1/100t 1/200 l	1/200 W. 1/400etw.W. Wirk.	1/200etw.
Br	Br	NO <sub>2</sub>	827	5813	1/800 t 1/1500l	1/1500o.W. o.W.	1/1500 o.W.
CH <sub>3</sub>	CH <sub>3</sub>	NHSO <sub>2</sub> -  -NO <sub>2</sub>	825	5811	1/100 t 1/200 l	1/200 o.W. o.W.	1/200 o.W.
CF <sub>3</sub>	CF <sub>3</sub>	NO <sub>2</sub>	830	5816	1/1500 t 1/3000 l	1/6000 o.W.	1/3000 o.W.
CF <sub>3</sub>	CF <sub>3</sub>	NH CO C <sub>3</sub> H <sub>7</sub>	838	5890	ab 1/50l	1/50o.W.	1/50o.W.
CF <sub>3</sub>	CF <sub>3</sub>	NH CO C <sub>6</sub> H <sub>5</sub>	839	5891	" 1/25l	1/25o.W.	1/25o.W.
CF <sub>3</sub>	CF <sub>3</sub>	NH-CO-CH-CH <sub>3</sub>   CH <sub>3</sub>	840	5892	1/200 t 1/400 l	1/400o.W.	1/400o.W.
CF <sub>3</sub>	CF <sub>3</sub>	NH-CO-CH <sub>2</sub> Cl	841	5897	ab 1/50l	1/50 o.W.	1/50 o.W.
CH <sub>3</sub> O	CH <sub>3</sub> O	NH <sub>2</sub>	völlig unwirksam				
NO <sub>2</sub>	NO <sub>2</sub>	NH-CO-CH <sub>3</sub>	"	"			
CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> NH <sub>2</sub>	"	"			
Cl	Cl	CH <sub>2</sub> NH <sub>2</sub>	"	"			
Br	Br	CH <sub>2</sub> NH <sub>2</sub>	"	"			

(\*) The following key explains the abbreviations in table:

W = effective                      etw.W.                      )  
 O.W. = no action                      etw.Wirk.                      ) = slight effect  
 Ohne Wirk. = No action etwas Wirk.                      )  
 völlig unwirksam = completely ineffective

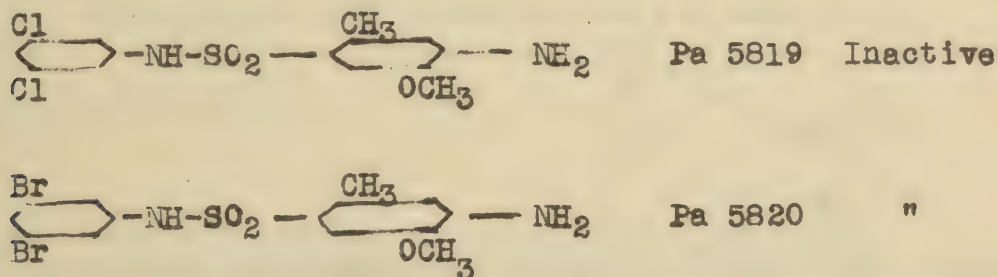
Furthermore, compounds with different positions of the halogen groups are completely inactive.



Compounds with 3 halogen atoms have a slight effect in 3, 4, 5 position.

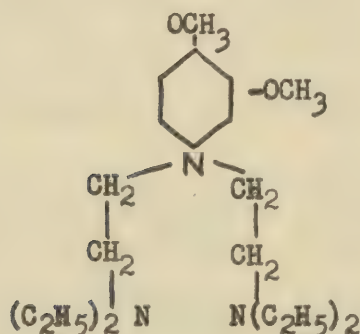
	<u>Toxicity (Pird)</u>	<u>Roehl's Test</u>	<u>Prophylactic Test</u>
$\begin{array}{c} \text{Cl} \\   \\ \text{C}_6\text{H}_3 \\   \\ \text{Cl} \end{array} \text{---NH-SO}_2\text{---C}_6\text{H}_4\text{---NH}_2$	1/50 t 1/100 l	1/200 W. 1/400 etw.W.	1/200 etw.W. 1/400 " W.
$\begin{array}{c} \text{Br} \\   \\ \text{C}_6\text{H}_3 \\   \\ \text{Br} \end{array} \text{---NH-SO}_2\text{---C}_6\text{H}_4\text{---NH}_2$	1/50 t 1/100 l	1/100 W. 1/200 etw.W.	1/100 " " 1/200 " "
$\begin{array}{c} \text{Cl} \\   \\ \text{C}_6\text{H}_3 \\   \\ \text{Cl} \end{array} \text{---NH-SO}_2\text{---C}_6\text{H}_4\text{---NHCOCH}_3$	1/25 t 1/50 l	1/200 W. 1/400 etw.W.	1/50 " " 1/100 " "
$\begin{array}{c} \text{Br} \\   \\ \text{C}_6\text{H}_3 \\   \\ \text{Br} \end{array} \text{---NH-SO}_2\text{---C}_6\text{H}_4\text{---NHCOCH}_3$	1/25 t 1/50 l	--	1/25 " " 1/50 " "

By introducing substituents into the benzol ring which bears the aromatic amino group inactive compounds are obtained.



A Summary of the Work on the Dimeplasmin Series.

Dimeplasmin is the name of a compound.

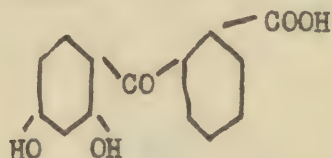


which was being tested as an antimalarial in 1927-28. The following table presents a comparison of the actions of this compound, quinine, and plasmochin on malaria in canaries:

	<u>Quinine</u>	<u>Plasmochin</u>	<u>Dimeplasmin</u>
	<u>hydrochloride</u>	<u>hydrochloride</u>	<u>base</u>
Smallest active dose	1:300	1:50000	1:3000
Largest tolerated dose	1:200	1:1500	1:100
Calculated range of effectiveness	1:4	1:30	1:30

On the average in comparison with plasmochin the toxicity in the rabbit, dog, and cat is ten times smaller, when administered intravenously or by mouth.

In the form of a salt of Reacid, with the following formula,



Dimeplasmin was tested at the Hamburg Tropeninstitut and in India on the three types of human malaria.

With doses of 8 tablets daily (= 0.8 g base), Prof. Mühlens, Hamburg, was unable to determine any effect.

In tertian malaria Col. Megan, Calcutta, observed no effect. In 4 cases of tropical malaria treated with the largest dosage (up to 2 g. base), Col. Knowles, Calcutta did not observe any favorable

results. One patient suffering from severe tropical malaria (treated with Dimeplasmin) died in coma after eight days (Green-Laucet 1929, No. 5518, p.1137)

Nausea appeared as a side reaction during treatment with large doses of Dimeplasmin.

At the suggestion of Dr. Röhl Dimeplasmin was also tested clinically for any effect it might have on amebic dysentery, but the result was negative.

The following is a brief presentation of experiences and observations in the investigation of this field.

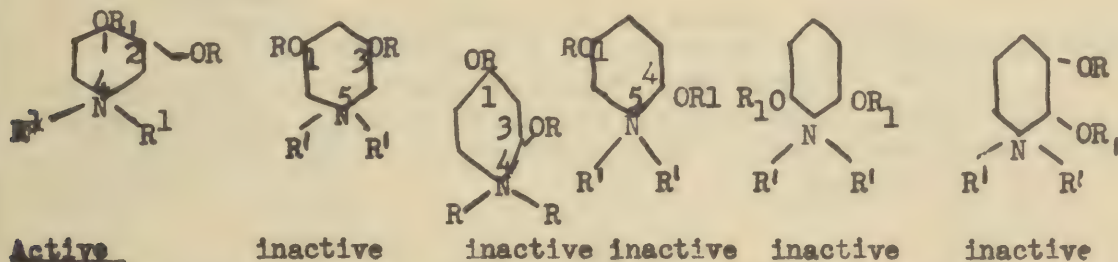
a. The varied oxygen-alkylations of the four N-basic-dialkylized aminopyrocatechindialkylethers were investigated. It was found that the alkyls (methyl, ethyl, isopropyl, propyl, isolutye, butyl, amyl) may be the same or different without any essential change in activity. However, if the sum of the carbon atoms on the two ether groups is 6 or more, the malarial activity is lost.

b. The position of the oxalkylgroups in relation to aromatic nitrogen.

After establishing that the 1,2-dialk-oxy-4-amino-position was essential for activity, the m-position in relation to nitrogen, that is, 1,3-dialkoxy-5-amino was investigated; the substances of this series are ineffective.

The other possible grouping, the 1,3 dialkoxy-4-amino position likewise shows no activity; this is also true of the 1,4 dialkoxy-5- amino position.

The last possible position that is 1,5-dialkoxy -6- amino, exhibits the same activity as Dimeplasmin.



$R = CH_3$ ;  $R_1 = CH(CH_3)_2$  ;  $R^1 = CH_2-CH_2-N(C_2H_5)_2$

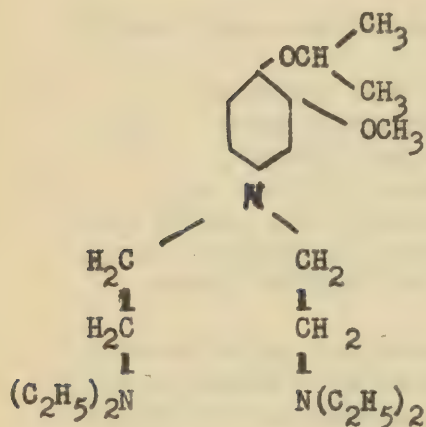
c. Other substitutions in place of the alkoxygroups.

When alkyls, carbon-alkoxy-halogen, or nitro groups were introduced in place of one or both alkoxygroups, the compounds were inactive.

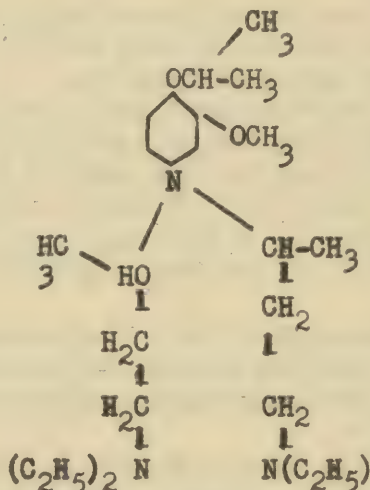
d. Influence of the basic alkyl groups (alkylreste).

After the influence of the oxygen alkylations acid the position of the alkoxy groups to aromatic nitrogen had been established, the various basic alkyl groups were investigated as to their activity.

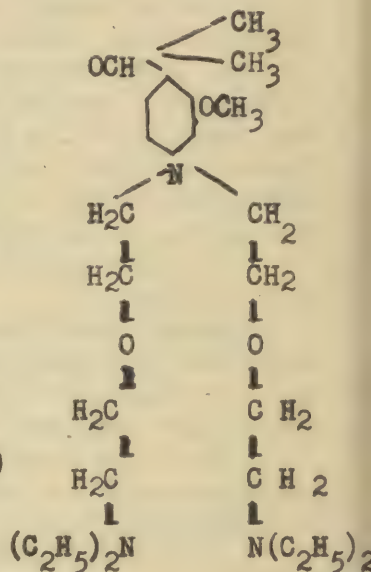
In contrast to the experience with the plasmochin series the surprising fact was observed that the aromatic nitrogen atom must be substituted twice by the basic group, and that only those basic alkyl groups are active which link the aliphatic nitrogen with the aromatic nitrogen by means of two C atoms. If this carbon chain has 3, 4, 5 C atoms, or if it is interrupted by oxygen, sulphur, or another N atom, the activity disappears.



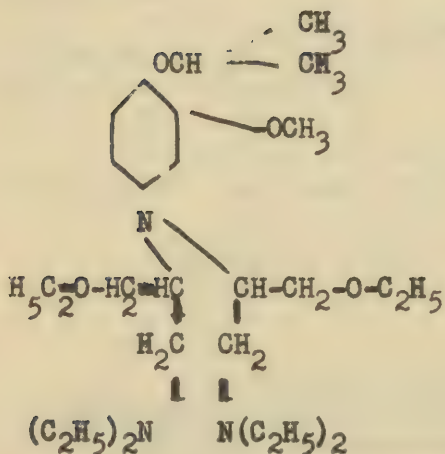
Active



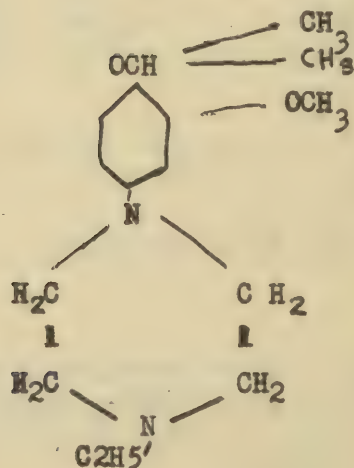
inactive



inactive



active



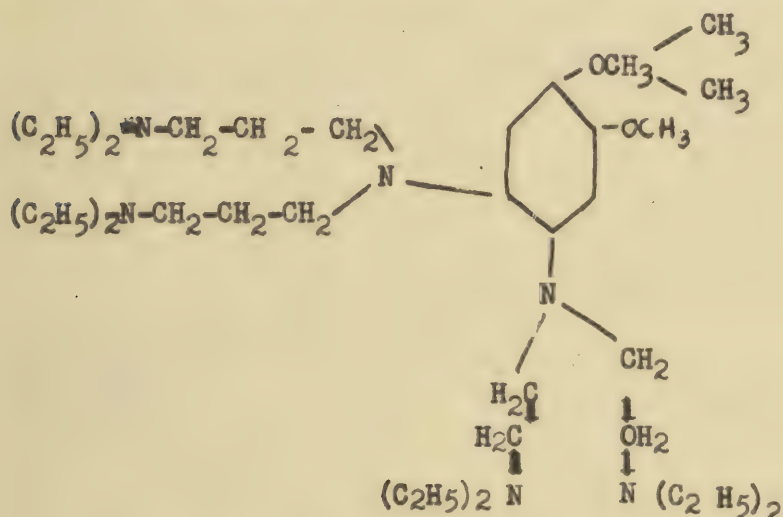
inactive

e. Influence of the alkyl groups of aliphatic nitrogen.

If amino-ethylchloride, dimethyl-aminoethylchloride, or propylamino-ethylchloride, etc. are used in place of diethylamino-ethylchloride for basic alkylation, the products remain active. However, if the sum of the carbon atoms on one of the substituted terminal nitrogen atoms is 6 or more, the antimalarial activity disappears.

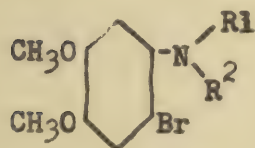
f. Aromatic o-diamines

Aromatic o-Dimines, which bear 2 alkoxy groups in p-position, continue to exhibit activity after basic dialkylation.

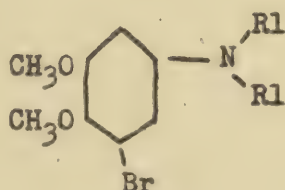


g. Further substitutions in the benzene nucleus.

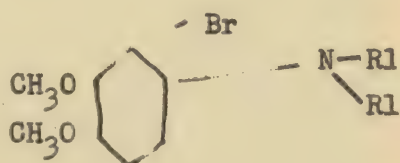
The introduction of a halogen atom in the benzene nucleus in o-position to the basic-substituted nitrogen atom produces an intensification of activity against avian malaria. The halogen atom, however, may not be situated in the neighborhood of an alkoxyl group.



active



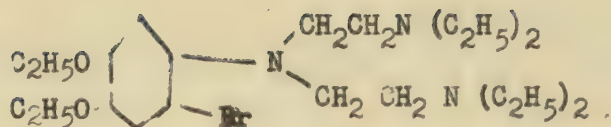
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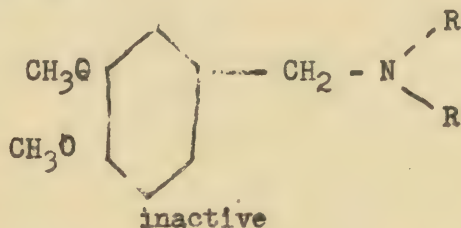
inactive

$R^1 = \text{CH}_2\text{-CH}_2\text{N}(\text{C}_2\text{H}_5)_2$

Diapromin=



H. Activity is dependent on aromatically bound nitrogen. If a carbon bridge is inserted between the benzene ring and nitrogen, activity disappears.



Elberfeld, 16 June 1930 signed Dir.Dr. Schönhöfer

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